ABSTRACTS OF WORLD MEDICINE

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Pathology

473. **Responses of the Liver to Injury. Effect of Previous Injury upon the Healing Pattern after Acute Carbon Tetrachloride Poisoning**

J. HOFFMAN, M. B. HIMES, A. KLEIN, V. POULOS, and J. POST. *A.M.A. Archives of Pathology* [*A.M.A. Arch. Path.*] **62**, 96–102, Aug., 1956. 2 figs., 8 refs.

The authors had previously found that healing of the liver after centrilobar necrosis due to carbon tetrachloride (CCl_4) poisoning was rapid in 8-week-old rats, being complete in 5 days, although excess nuclear polyploidy was still detectable 8 weeks later. At Columbia University, New York, they have now performed on young rats further experiments designed to ascertain whether such previous injury to the liver affected the rate of recovery from subsequent damage due to CCl_4. These showed that after a second injection of CCl_4 8 weeks after the first the rate of recovery, as indicated by mitotic activity and the level of tissue nucleic acids, was delayed significantly, the histological appearances in the liver at 120 hours being similar to those 72 hours after the primary injury. Moreover, octaploidy was twice as frequent, being observed in 7 to 9% of animals after the first injury and in 15 to 17% after the second injury.

These findings are discussed in the light of the known association between previous liver damage and cancer of the liver, and of the important role of polyploidy in carcinogenesis. Their possible importance in the pathogenesis of chronic liver disease is also stressed.

J. B. Cavanagh

CHEMICAL PATHOLOGY

474. **Calcium Concentrations in Sclerotic Cerebral Arteries**

J. C. PATERSON and B. R. CORNISH. *A.M.A. Archives of Pathology* [*A.M.A. Arch. Path.*] **62**, 177–182, Sept., 1956. 9 refs.

It has been reported that even in the presence of severe atherosclerosis the concentration of calcium in the cerebral arteries may be unusually low. The authors have therefore examined necropsy material from 71 chronically ill patients dying at Westminster Hospital (Department of Veterans Affairs), London, Ontario, in which the grade of atherosclerosis in the coronary, cerebral, and femoral arteries and in the abdominal aorta was assessed by a number of indices, including the concentration of lipid and calcium in each type of vessel as well as the degree of stenosis due to the largest plaque. Fresh tissues were subjected to alkaline digestion and analysed for total lipid content, and also to acid digestion and analysed for calcium content. Morphological and chemical estimations were carried out independently by two groups of workers. The concentrations of lipid and calcium in severe, moderate, and slight grades of sclerosis were compared statistically.

The results of the investigation were as follows. (1) The concentration of calcium in severely sclerotic cerebral arteries was negligible, but was appreciable in severely affected coronary arteries; the concentration in cerebral vessels showing moderate or slight sclerosis was considerably lower than in coronary vessels affected to a similar degree. The difference in the degree of calcification between coronary and cerebral arteries was so marked as to be obvious on cutting the vessels with a knife. (2) There was a significant increase in lipid concentration in both cerebral and coronary arteries with increasing severity of atherosclerosis. (3) The calcium concentration increased significantly with increasing severity of sclerosis in the coronary arteries, but not in the cerebral arteries.

The mean age of the patients with differing degrees of coronary sclerosis was not significantly different from that of those with comparable degrees of cerebral sclerosis. However, age appeared to be a factor in the progression of cerebral sclerosis, but not in that of coronary sclerosis. The authors suggest that the defective calcification in sclerotic cerebral arteries may explain why they are more liable to rupture than are other arteries.

Robert de Mowbray

475. **Serum Concentrations of Vitamin B_{12} in Acute and Chronic Liver Disease**

M. RACHMILEWITZ, J. ARONOVITCH, and N. GROSSOWICZ. *Journal of Laboratory and Clinical Medicine* [*J. Lab. clin. Med.*] **48**, 339–344, Sept., 1956. 10 refs.

The authors, from the Hadassah Medical School, Jerusalem, have previously (*Harefuah*, 1955, **49**, 267) reported a rise in serum level of vitamin B_{12} (cyanocobalamin) in cases of cirrhosis of the liver and other types of hepatic damage. They now report further results of serial estimations in chronic liver disease. Cyanocobalamin levels were determined by a modified *Escherichia coli* assay in 25 healthy individuals and in 31 patients with liver disease and correlated with the results of the usual liver function tests and electrophoretic serum protein values. High cyanocobalamin values were

found in the serum of 13 out of 14 patients with acute viral hepatitis, in 5 cases of biliary cirrhosis, and in 3 out of 6 cases of portal cirrhosis. In 6 patients with extrahepatic biliary obstruction and jaundice the level was normal. Although the cause of this rise in serum cyanocobalamin level in liver disease is uncertain, it is suggested that release of the stored vitamin from damaged liver cells is responsible. *A. Wynn Williams*

476. **The Clinical Significance of the Analysis of Serum Protein Distribution by Filter Paper Electrophoresis**
W. P. JENCKS, E. R. B. SMITH, and E. L. DURRUM. *American Journal of Medicine* [*Amer. J. Med.*] **21**, 387–405, Sept., 1956. 2 figs., 46 refs.

The results of the filter-paper electrophoretic analysis of the serum protein pattern in 1,516 patients on whom complete clinical data and the final diagnosis were available at the Walter Reed Army Medical Center, Washington, D.C., were studied in order to provide information on (1) the normal range of distribution of serum protein fractions as measured by this method, (2) the type, incidence, and diagnostic significance of variations from the normal of serum protein distribution in disease, and (3) the clinical usefulness of the technique. The differences between results obtained by paper and by moving-boundary electrophoresis, and the reasons for these differences, are discussed. The results of the filter-paper electrophoresis are analysed in relation to various diseases in order to determine the incidence and nature of serum protein abnormality in various disease groups, and then according to type of abnormality in order to determine the kinds of disease and diagnostic significance associated with each type of abnormality.

The proportional distribution of serum proteins in 185 "normal" subjects (70 with no apparent disease, 24 with minor injuries, 40 with localized mild skin disease, and 51 with deafness) were as follows: albumin 60 to 77% (average 68·9%); α_1 globulin 1 to 5% (average 2·9%); α_2 globulin 4 to 10% (average 7·3%); β globulin 5 to 13% (average 9·0%); and γ globulin 7 to 17% (average 12·0%). Infectious diseases (187 patients, of whom 22 were suffering from tuberculosis), malignant neoplasms (76 patients), arteriosclerosis (58), rheumatic heart disease (18), hepatitis (24), hepatic cirrhosis (3), rheumatoid arthritis (27), and sarcoidosis (8 patients) were frequently associated with an abnormal serum protein distribution. The most frequent abnormalities in a group of 965 patients were a decrease in serum albumin concentration (143 patients), and increases in the concentrations of α_2 globulin (104 patients), γ globulin (60 patients), β globulin (35 patients), and α_1 globulin (26 patients). Increased serum albumin values (3 patients) and decreased serum globulin values (13 patients) were rarely found. The serum protein distribution in 325 women post partum and in 41 newborn infants are also reported.

In conclusion it is suggested that paper electrophoretic analysis of the serum proteins may be pathognomonic of multiple myeloma, nephrosis, and hypogammaglobulinaemia, and useful in the diagnosis of hepatitis, cirrhosis, tuberculosis, sarcoidosis, kala-azar, and lymphogranuloma venereum. In addition it can provide information on the state of disturbed physiological conditions, and activity and, occasionally, the diagnosis of rheumatoid arthritis, rheumatic fever, malignancy, and the sequelae of arteriosclerosis and infectious diseases.

J. E. Page

477. **Enzyme Test for Glycosuria**
R. E. TUNBRIDGE, R. G. PALEY, and D. COULSON. *British Medical Journal* [*Brit. med. J.*] **2**, 588, Sept. 8, 1956.

The paper-strip enzyme test for glucose in urine ("tes-tape") has been tested at the University of Leeds against the figures obtained by another commercial test ("clinitest") in samples of urine obtained at a diabetic clinic. There was close agreement between the two tests when the concentration of sugar was less than 0·1 g. per 100 ml., but at higher glucose concentrations greater discrepancies occurred; 7% of tests showing 2 g. per 100 ml. by clinitest gave less than 0·5 g. by tes-tape; 4% were negative for glucose by clinitest when 0·5 to 2 g. was recorded by testape. It is concluded that the test can be of no use in the management of diabetes, since 11% of tests are so misleading as to be likely to confuse the patient. *C. L. Cope*

HAEMATOLOGY

478. **The Inhibition of Thrombin Formation by Heparin.**
(Inhibition de la thrombinoformation par l'héparine)
M. BURSTEIN and J. LOEB. *Revue française d'études cliniques et biologiques* [*Rev. franç. Ét. clin. biol.*] **1**, 752–758, Sept., 1956. 30 refs.

The authors, working at the French National Blood Transfusion Centre, Paris, have investigated the mechanism by which heparin inhibits blood clotting. Their test system consisted of recalcified heparinized human euglobulin, which contains fibrinogen and also prothrombin with its various activating factors. Prolongation of the coagulation time of this system is due to inhibition of thrombin formation.

A comparison was made between the co-factor (in the presence of which heparin blocks thrombin formation and which is present in defibrinated prothrombin-free plasma) and purified bovine antithrombin. Both were shown to be thermolabile and both were absorbed by aluminium hydroxide and tricalcium phosphate and destroyed by chloroform. Also both were consumed during the inactivation of thrombin, particularly in the presence of heparin. Both substances were found to be α_2 globulins and could not be separated by fractionation methods; further, the co-factor and antithrombin were found in equal concentrations in the same plasma fraction. The authors therefore conclude that the plasma co-factor which, in the presence of heparin, inhibits the conversion of prothrombin to thrombin is identical with antithrombin.

In a previous paper one of the authors (Burstein, *Arch. Internat. Pharmacodyn.*, 1955, **101**, 28) showed that the plasma co-factor which inhibits the formation of fibrin

from fibrinogen in the presence of heparin is also antithrombin. The authors suggest that heparin increases the affinity of antithrombin for thrombin, thus leading to a very fast inactivation of the latter by heparinized plasma, and that this causes prolongation of the thrombin time. *B. Ruebner*

479. **The Macrocytosis of Liver Disease**
C. A. HALL. *Journal of Laboratory and Clinical Medicine* [*J. Lab. clin. Med.*] **48**, 345–355, Sept., 1956. 6 figs., 28 refs.

The author reports from the Veterans Administration Hospital, Albany, New York, a study of the morphological and numerical changes in the erythrocytes in cases of diffuse hepato-cellular damage. Haematological and liver function tests were repeated weekly or bi-weekly in 24 cases of Laennec's cirrhosis, 5 of severe chronic alcoholism without clinical or laboratory evidence of liver disease, 3 of severe viral hepatitis, 2 of secondary carcinomatosis of the liver, and one case of hepatoma without cirrhosis. Non-anaemic cases were included, but not cases with anaemia due to haemorrhage. Erythrocyte diameters were determined by the direct photographic method of Larsen (*Acta med. scand.*, 1948, **132**, Suppl. 220). The results showed that liver damage is usually accompanied by an increase in the mean erythrocyte diameter. The macrocytosis is often present without anaemia, and its degree can be roughly correlated with the results of liver function tests. Its cause is not understood, but it may be significant that the erythrocyte frequency distribution curves of liver disease resemble those of pernicious anaemia in partial remission. *A. Wynn Williams*

MORBID ANATOMY AND CYTOLOGY

480. **Degenerative Changes in Ciliated Cells Exfoliating from the Bronchial Epithelium as a Cytologic Criterion in the Diagnosis of Diseases of the Lung**
G. N. PAPANICOLAOU. *New York State Journal of Medicine* [*N.Y. St. J. Med.*] **56**, 2647–2650, Sept. 1, 1956. 30 figs., 8 refs.

The author, from Cornell University Medical College, New York, records his observations on mass degeneration and destruction of the ciliated cells of the bronchial mucosa, a phenomenon which he calls "ciliocytophtoria". He describes, with illustrations, the cytological features most frequently encountered—namely, the broken-off anucleated tips of ciliated cells, the pinched-off tufts, the nucleated basal fragments deprived of their distal ciliated portions, the characteristic pattern of the degenerating nuclei displaying deeply-staining chromatin clumps arranged along the nuclear membrane, and the total absorption of nuclei and nuclear phagocytosis by polymorphonuclear leucocytes and histiocytes. In some cases eosinophil cytoplasmic inclusions of obscure nature are noted. These changes were demonstrated in about 300 cases—preponderantly cases of acute respiratory illness such as pneumonia and pneumonitis, bronchitis, and influenza, but also of chronic conditions such as asthma and bronchiectasis. During periods of symptomatic improvement the exfoliation of atypical ciliated cells decreased, as a rule considerably. It is interesting that in a rather large proportion of cases (12%) the presence of a bronchogenic carcinoma was subsequently established. *R. Salm*

481. **The Lungs in Mitral Stenosis.** (Die Lunge bei der Mitralstenose)
H. MEESSEN. *Deutsche medizinische Wochenschrift* [*Dtsch. med. Wschr.*] **81**, 1445–1448, Sept. 7, 1956. Bibliography.

The author of this paper from the Institute of Pathology of the Düsseldorf Academy of Medicine confirms the finding of previous workers that post-mortem angiography in cases of mitral stenosis shows a widening and increased tortuosity of the pulmonary arteries, their lumen decreasing towards the periphery not gradually, but in a series of steps. Similar changes are demonstrable in the pulmonary veins. The associated histological changes in the pulmonary vessels have been studied at necropsy in 62 cases of pure mitral stenosis and in 200 biopsy specimens of the left lung obtained during mitral valvotomy. The operation specimens showed distinct hypertrophy of the media and increase in the number of elastic lamellae; the adventitia was dense and the intima thickened by the development of loose, oedematous connective tissue. Precapillaries often showed multiplication of the muscle fibres, which might undergo hyalinization. The veins showed intimal thickening, sometimes involving the whole wall and associated with irregular fibrosis. In some cases of mitral stenosis these vascular changes precede any change in the parenchyma; they explain the dearth of small vessels in the post-mortem angiogram and also the step-like changes in the calibre of the larger vessels.

The author points out that while muscular hypertrophy in the vessel walls may be reversible, the development of fibrosis produces "fixation of increased pulmonary pressure", which may detract from the benefit of operation.

The firm consistency of the lung in mitral stenosis is due to thickening of the alveolar septa by collagen and elastic fibres. Electron microscopy demonstrates a marked increase in the thickness of the epithelial lining of the alveoli and the presence of numerous fine fibrils. *F. Hillman*

482. **Changes in the Intramural Coronary Branches in Coronary Arteriosclerosis**
O. SAPHIR, L. OHRINGER, and R. WONG. *A.M.A. Archives of Pathology* [*A.M.A. Arch. Path.*] **62**, 159–170, Aug., 1956. 7 figs., 13 refs.

Although cholesterol metabolism now receives most of the attention in discussions of coronary arteriosclerosis, the present authors consider that the earlier concept of inflammation as at least one of the causal factors may help in certain cases to explain the relatively early onset of coronary sclerosis and myocardial changes, the incidence of which in younger persons has nearly doubled in the last 15 years.

At the Michael Reese Hospital, Chicago, they have therefore examined microscopically the myocardium and particularly the intramural coronary branches in 100 patients (68 males) under the age of 50 dying of arterio- or atherosclerosis. This revealed that in 82 cases there was perivascular or vascular fibrosis, with or without cellular infiltrates suggestive of old arteritis. Among these were 18 cases of hypertension, 7 of diabetes, and 10 of endocarditis, while there was a history of rheumatic fever in 2 cases, of chronic infectious disease (including 10 cases of nephritis or nephrosis) in 15, and of hypersensitivity [nature of allergy unstated] in 12. The authors suggest that the increased incidence of these coronary arterial changes in patients in the 3rd, 4th, and 5th decades of life may be related to a state of hypersensitivity, which may be not unconnected with the greatly increased use of antibiotic and chemotherapeutic agents in recent years. *J. B. Cavanagh*

483. **Structural Changes in the Heart Resulting from Cardiac Massage**
G. H. PEDDIE, O. CREECH, and B. HALPERT. *Surgery* [*Surgery*] **40**, 481–487, Sept., 1956. 7 figs., 8 refs.

Structural changes observed in the hearts of 14 patients who were treated by cardiac massage for cardiac arrest are reported. The reaction of the pericardium was a progressive pericarditis independent of the duration or technique of massage. When the massage was prolonged over 15 minutes the myocardial damage was moderate to severe. Rupture of the myocardium occurred in one instance after 90 minutes of massage. —[Authors' summary.]

484. **Needle Biopsy of the Liver in Cirrhosis. Diagnostic Efficiency as Determined by Postmortem Sampling**
H. BRAUNSTEIN. *A.M.A. Archives of Pathology* [*A.M.A. Arch. Path.*] **62**, 87–95, Aug., 1956. 4 figs., 43 refs.

From a survey of the literature the author concludes that the transcutaneous needle biopsy technique is generally agreed to be diagnostically reliable in diffuse liver conditions, such as viral hepatitis, fatty liver, amyloidosis, and obstructive jaundice, and despite implications to the contrary it is also of considerable value in cases of tumour of the liver. Its usefulness, however, has been questioned in hepatic cirrhosis.

In tests carried out at Cincinnati University College of Medicine the liver from 30 patients dying of various types of cirrhosis was removed at post-mortem examination and specimens of hepatic tissue were taken with a Vim–Silverman needle from 18 standardized areas, 12 in the right lobe and 6 in the left, over the surface of the liver, a total of 507 specimens suitable for appraisal being thus obtained.

In 13 cases of nutritional cirrhosis (224 specimens) there were no false negative results on examination of the specimens. Among 131 samples from 8 cases of postnecrotic cirrhosis 5 false negative results were obtained, while a further 5 false negative samples were found among 152 from 9 cases of post-hepatitic cirrhosis. It is concluded that needle biopsy is in fact a highly accurate diagnostic method for the recognition of hepatic cirrhosis. The author points out, however, that as a means of estimating the severity of the process and of following its progression or regression " accuracy may be assumed only in the case of nutritional cirrhosis ". *J. B. Cavanagh*

485. **The Intestinal Tract in Diabetic Diarrhea. A Pathologic Study**
K. G. BERGE, R. G. SPRAGUE, and W. A. BENNETT. *Diabetes* [*Diabetes*] **5**, 289–294, July–Aug., 1956. 19 refs.

The clinical and pathological features of so-called diabetic diarrhoea, as seen in 8 cases at the Mayo Clinic, are described. The condition is characterized by an intermittent diarrhoea associated with urgency, tenesmus, and nocturnal exacerbations. The patients, whose ages ranged from 18 to 72 years (mean 53 years), were severely diabetic, control of the diabetes being poor in 5. Retinopathy and neuropathy were present in 7 and albuminuria was noted in 4. Little abnormality was found in the intestines; fibrosis of the outer muscle coat of the jejunum, which was thickened, was seen in one case and similar fibrosis in the colon in another. Other findings were polypi in the transverse and sigmoid colon in one case and small rectal ulcers in one. Particular attention was paid to the nerve cells of the enteric plexuses, but although a certain number of pyknotic or chromatolytic cells were observed, they were no more frequent in these patients than in diabetics without diarrhoea or in non-diabetic subjects. The authors do not consider, therefore, that they found any morphological basis for the diarrhoea of diabetes, and, in particular, no evidence in support of the hypothesis that this diarrhoea has a neurogenic basis. *M. C. Berenbaum*

486. **The Glomerular Lesions of Diabetes Mellitus. Cellular Hyaline and Acellular Hyaline Lesions of " Intercapillary Glomerulosclerosis " as Depicted by Histochemical Studies**
E. E. MUIRHEAD, P. O. MONTGOMERY, and E. BOOTH. *A.M.A. Archives of Internal Medicine* [*A.M.A. Arch. intern. Med.*] **98**, 146–161, Aug., 1956. 11 figs., bibliography.

Two hyaline lesions are observed within the glomeruli of kidneys of diabetic subjects. One lesion tends to be nodular and is both cellular and collagenous. For this structure the term " cellular hyaline lesion " is preferred. The other lesion is crescentic, globular, oval, or elongated and is acellular. It has the same appearance as the hyalin of arteriosclerosis. For this structure the term " acellular hyaline lesion " is preferred. The " cellular hyaline lesion " is commoner than the " acellular hyaline " structure. In some kidneys, however, one lesion is as often encountered as the other.

The " acellular hyaline lesion " displays the staining characteristics of " fibrinoid ". A series of histochemical procedures applied to this substance demonstrates the presence of multiple ingredients, such as triglycerides, fatty acids; phosphatides, cholesterol, and its esters; aldehyde groups likely associated with poly-

saccharides, mucopolysaccharides, mucoproteins, glycoproteins, glycolipids, or unsaturated lipids; sulfuric acid esters of polysaccharide origin; free carbonyl groups; free potassium, and protein-bound sulfhydryl groups. The " cellular hyaline lesion " has the staining characteristics of collagen. The above histochemical procedures with this structure yield either negative or minimal results, except for the periodic-acid–Schiff reagent procedure, which is positive. The staining and histochemical characteristics of the " acellular hyaline lesion " are identical with those of the hyalin of hyaline arteriosclerosis. The disposition of the " acellular hyaline material " is considered in keeping with an intracapillary position. It is suggested that the glomerular " acellular hyaline masses " are derived from the hyalin of the arteriole by embolization. Rupture of the material through the capillary wall can account for its presence in Bowman's space and certain tubules.

Reasons have been cited for the view that vascular " fibrinoid " is derived from altered smooth muscle of the media. The considerations of the present study suggest a similar origin from smooth muscle for the " acellular hyaline lesion " of the glomerulus of diabetic subjects. The pathogenetic relationship between the " cellular hyaline " and " acellular hyaline " glomerular lesions of diabetes remains obscure.—[From the authors' summary.]

487. **A Pathological Study of Five Cases of Pyelonephritis in the Newborn**

K. A. PORTER and H. MCC. GILES. *Archives of Disease in Childhood* [*Arch. Dis. Childh.*] **31**, 303–309, Aug., 1956. 5 figs., 15 refs.

In this paper from St. Mary's Hospital, London, the necropsy findings in 5 cases of pyelonephritis occurring in male infants under one month of age are described. One patient died during the acute phase of the illness, 2 died later in uraemia, and 2 succumbed to intercurrent infections. In the infant who died after an acute illness of relatively brief duration the kidneys showed the typical histological picture of acute pyelonephritis, differing in no way from that seen in older children or in adults. However, in the remaining 4 cases the kidneys differed in two respects from those of adults suffering from chronic pyelonephritis. (1) Macroscopically, there was little asymmetrical contraction or coarse shallow scarring. This may have been due to the comparatively short time during which the pyelonephritic process had been in progress, since all the patients were under 21 weeks of age at the time of death. (2) Microscopically, epithelial crescents in varying numbers were present. The authors point out that this does not necessarily exclude the diagnosis of chronic pyelonephritis, since crescents are known to occur in diseases other than glomerulonephritis. On examination of the kidneys by microdissection, abnormalities were found in the nephron in 4 of the patients, 2 of whom were brothers. The authors suggest that congenital abnormalities of the nephron may play an important role in predisposing such infants to renal infection.

The majority of infants with acute pyelonephritis apparently recover, but in a few instances the renal disease may ultimately cause hypertension, bone lesions, renal failure, or a combination of these. It is urged that pyelonephritis should be considered as a possible diagnosis in any infant who vomits, loses weight, or goes off his food. Further, it is recommended that known cases of pyelonephritis should be followed up with care and even apparently minor abnormalities in the urine of these patients should not be too readily disregarded.

A. W. H. Foxell

488. **Histopathology of Cutaneous Lesions in Systemic Lupus Erythematosus**

M. PRUNIÉRAS and H. MONTGOMERY. *A.M.A. Archives of Dermatology* [*A.M.A. Arch. Derm.*] **74**, 177–190, Aug., 1956. 4 figs., 41 refs.

The authors report from the Mayo Clinic the results of a histopathological study of the cutaneous lesions in 38 cases of systemic and 3 cases of chronic discoid lupus erythematosus (L.E.).

The diagnostic changes, which are described, included follicular plugging, hyperkeratosis but no parakeratosis, liquefactive degeneration of the basal layer, and lymphocytic infiltration. Fibrinoid changes in the vessels were not frequent (5 out of 38 cases), and aggregates of karyorrhexic nuclei even less so (2 out of 38 cases). Differentiation between systemic and chronic discoid forms of L.E. has been found almost impossible, the histological changes being related more to the age of the lesions than to the clinical type of the disease. The diagnostic features became clear when the lesions were about 4 weeks old, but up to this time the histological changes were non-specific.

The basement membranes of the epidermis, hair follicles, and sweat glands stained strongly positive with periodic-acid–Schiff and were swollen or fragmented. The histiocytes in these situations revealed intense macrophagic activity. An increase in the numbers of mast cells was also observed. Performance of a modified Brachet test (methylpyronine stain controlled by ribonuclease and perchloric acid extraction) demonstrated the presence of " red bodies " derived from the nuclei of lymphocytes and to a lesser extent from those of connective-tissue cells through depolymerization of deoxyribonucleic acid; these " red bodies " appear to be non-specific for L.E. On the other hand metachromasia, as revealed by staining with toluidine blue, occurring both intracellularly and extracellularly, is considered to be characteristic of the disease. Staining was controlled by the use of hyaluronidase, acetylation, sulphation, and oxidation by chromic acid; the results were found to be suggestive of a pathological modification in the synthesis of mucopolysaccharides by the connective-tissue cells. Sudan black B showed round cytoplasmic inclusions in macrophages in 5 out of the 38 cases.

A. Swan

489. **An Electron Microscopic Study of the Ground Substance of Connective Tissue**

A. M. ASADI, T. F. DOUGHERTY, and G. W. COCHRAN. *Nature* [*Nature (Lond.)*] **178**, 1061–1062, Nov. 10, 1956. 6 figs., 7 refs.

Microbiology and Parasitology

490. **Administration of Live Influenza Virus to Volunteers**
A. Isaacs and A. T. Roden. *Lancet* [*Lancet*] **2**, 697–699, Oct. 6, 1956. 22 refs.

If a pandemic of severe influenza were to occur, it is likely that attempts would be made to produce a formalin-killed vaccine from the prevailing strain of virus. The dose for the production of such protection as these vaccines offer is approximately the amount of virus yielded by one fertile hen's egg. The amount of vaccine available would thus be small in relation to probable requirements. If, however, a live, attenuated virus vaccine could be developed it is likely that a much smaller dose of virus would be required to initiate the subclinical immunizing infection. An investigation was carried out at the Common Cold Research Unit, Salisbury, to determine whether human beings could be infected with recently isolated strains of influenza-A virus which had undergone relatively few passages in the chick embryo, 17 volunteers being inoculated intranasally or by throat spraying with two strains of influenza-A virus isolated in England in 1953. All the strains had undergone one amniotic passage and one, four, or ten allantoic passages. The inoculum contained between 10^4 and $10^{5\cdot6}$ egg-infective doses. No clinical signs of upper respiratory infection developed in any of the subjects and there was no increase in either haemagglutination-inhibiting or complement-fixing antibody in the serum. The haem-agglutination-inhibiting titres before inoculation were low in all but one of the subjects. No virus was recovered from garglings collected 2 to 5 days after inoculation. It was concluded that the influenza-A virus on allantoic passage rapidly loses its ability to multiply in man. *J. E. M. Whitehead*

491. **Certain *in vivo* and *in vitro* Observations on *M. tuberculosis*. Their Application in the Public Health Laboratory**
L. R. Peizer, D. Widelock, and S. Klein. *American Review of Tuberculosis and Pulmonary Diseases* [*Amer. Rev. Tuberc.*] **74**, 428–437, Sept., 1956. 24 refs.

At the laboratories of New York City Department of Health the authors have studied the cultural behaviour of isoniazid-resistant strains of *Mycobacterium tuberculosis* and the virulence of these strains for guinea-pigs and mice. Cultures were made from 300 specimens of sputum known to be positive which were obtained from patients under treatment with isoniazid, concentrated with trisodium phosphate, and inoculated on to Löwenstein–Jensen medium and on two types of eggless agar–charcoal media, one of which contained serum. On the egg-yolk medium 97% of cultures were positive and on the medium containing serum 95% were positive after 4 weeks at 37° C., whereas on the charcoal medium only 56% were positive after 10 weeks. The addition of 5% carbon dioxide to the atmosphere did not significantly increase the percentage of positive cultures obtained, so that carbon dioxide does not appear to be essential for the growth of tubercle bacilli if egg-yolk or serum is present in the medium.

Of 35 isoniazid-resistant strains of tubercle bacillus which were tested for their degree of resistance before and after 20 transplants on drug-free medium, 10 were catalase-negative and their degree of resistance to isoniazid remained unchanged, whereas of the 25 catalase-positive strains, the majority showed a tendency to regression of resistance. When 13 of the catalase-positive, isoniazid-resistant strains were inoculated into guinea-pigs they produced progressive tuberculosis, but only after a delay of several weeks in which the disease, though present, was not of great severity. However, 4 strains of catalase-negative, isoniazid-resistant bacilli injected into guinea-pigs either killed them within 3 weeks or, in those animals surviving, caused slight visceral lesions only, which had regressed by 6 weeks. Further studies in mice showed that the degree of virulence of both groups of tubercle bacilli for this species was nearly the same. *John M. Talbot*

492. **The Significance of Antigen–Antibody Reactions in Tuberculosis**
F. B. Seibert. *Journal of Infectious Diseases* [*J. infect. Dis.*] **99**, 76–83, July–Aug., 1956. 15 refs.

The purpose of this work, carried out at the University of Pennsylvania, Philadelphia, was to investigate the possibility that antigens derived from tubercle bacilli and the antibodies to them are present in combination in tuberculous caseous material, and also to determine whether this antigen–antibody complex, if present, is soluble in excess antigen or in high concentrations of sodium chloride. Extracts were made from: (1) the lungs of 2 guinea-pigs infected with a virulent human strain of tubercle bacillus; (2) the lungs of a rabbit which died with extensive disease after intravenous inoculation with a virulent bovine strain of the bacillus; (3) the lungs of a rabbit which had been sensitized by 15 weekly intravenous injections of 0·25 mg. of live B.C.G. organisms, then infected intravenously with 0·0005 mg. of a virulent bovine strain of tubercle bacillus, and finally given 13 weekly injections of tuberculoprotein; and lastly (4) material from two large caseous cysts present in the abdomen of a rabbit infected with the bovine strain mentioned in (2) above. The extracts were made first with 0·9% saline, then with 20% saline, and finally the residue mixed with water, autoclaved, and the supernatant passed through a Seitz filter.

By means of precipitin tests with tuberculoprotein and tuberculopolysaccharide, and also with the corresponding antisera, the presence of both tuberculous antigen and

antibody was confirmed in extracts from caseating lung and in the caseous material from the abdominal cysts. Certain of the extracts of the caseous material were insoluble in 0·9% saline, but soluble in 20% saline. These extracts were also partially soluble in excess tuberculopolysaccharide and tuberculoprotein, in these respects resembling artificially prepared antigen–antibody complexes. It is suggested that a similar process may occur in tuberculous tissue in the body, and that the solution of precipitates of the antigen–antibody complex by excess antigen may play a part in the phenomena of caseation and liquefaction in tuberculosis.

John M. Talbot

493. **Studies in Pertussis Immunity. III. Immunization of Children with Live and Killed Vaccine. IV. Booster Response in Man Induced by Various Fractions of *H. pertussis***

J. L. WINTER. *Proceedings of the Society for Experimental Biology and Medicine* [*Proc. Soc. exp. Biol. (N.Y.)*] 92, 832–835 and 835–838, Aug.–Sept., 1956. 3 figs., 3 refs.

In the first of the two studies on immunization against whooping-cough here reported from New York University College of Medicine the efficacy of live and killed vaccines of *Haemophilus pertussis* in the immunization of 40 mentally defective children, ranging in age from 9 months to 11 years, at an institution in New York State was compared, half the children being given a live vaccine, and half a vaccine in which the organisms had been killed by the addition of thiomersalate. Each ml. of the vaccine contained 20,000 million organisms, and an initial injection of 0·5 ml. was followed by three injections of 1 ml. each at monthly intervals, given into the buttock in younger children and into the deltoid muscle in older ones. Blood from the patients was obtained before the first inoculation, 4 weeks after the second, and 2 months after the final injection, and the serum injected intraperitoneally into mice, which were then challenged with live *H. pertussis* intranasally.

In the patients receiving the live vaccine a number of severe reactions occurred, some of which persisted for as long as 3 weeks. The results of the mouse-protection tests and of antibacterial agglutinin titre determinations showed that a number of the children responded poorly to both types of vaccine and that there was no essential difference between the two. No opportunity occurred of testing the possible protective power of the vaccines against natural infection with whooping-cough.

In the second of these studies, as it had been shown previously that a high percentage of adults respond to a booster injection of killed pertussis organisms by a sharp rise in the titre of mouse-protection antibody, the author attempted to confirm this by injecting 100 adults at the same institution not only with a vaccine made from whole *H. pertussis* organisms, but also from four different fractions of the bacillus as follows: (1) the agglutinogen fraction of Smolens and Mudd; (2) the protective antigen of Pillemer; (3) the haemagglutinin of Keogh and North; and (4) the soluble fraction of Pennell and Thiele. Five groups, each of 20 persons, were given either the whole killed vaccine or one of the four fractions in a dose of 0·5 ml. and the response tested by determination of antibacterial agglutinins in the subject's serum and by the passive-protection test in mice. It was found that only the soluble antigen fraction and the haemagglutinin fraction gave as good protection as the whole vaccine against intranasal challenge.

The author concludes that while only extensive field trials can provide a definite answer to this problem, it seems at present that multiple antigens are likely to be more suitable than single ones, and that the value of those which give poor results in mouse-protection tests is questionable.

[In the first study reported above, which was based on only 40 children, the author expresses a doubt whether mental defectives as a group are as readily immunized as the general population. Surely a great deal more evidence must be accumulated before any such assertion can be made.] *W. K. Dunscombe*

494. **The Use of Anthrax Antigen to Immunise Man and Monkey**

H. M. DARLOW, F. C. BELTON, and D. W. HENDERSON. *Lancet* [*Lancet*] **2**, 476–479, Sept. 8, 1956. 5 refs.

An investigation was carried out at the Microbiological Research Establishment, Porton, Wiltshire, with the object of testing the reaction of man to repeated injections of anthrax vaccine and to observe in monkeys the duration of immunity induced by two subcutaneous injections. The vaccine was prepared by the method of Belton and Strange (*Brit. J. exp. Path.*, 1954, **35**, 153; *Abstracts of World Medicine*, 1954, **16**, 444), the antigenic activity of this alum-precipitated material being then assessed by active immunization tests in rabbits. One group of 10 monkeys given two doses of a vaccine which had been used for immunizing man were challenged 7 days after the second dose; all survived, whereas 10 control animals were dead by the sixth day. A second group of 10 monkeys were immunized in the same way and challenged after one year; all survived. Of a third group of 10 monkeys similarly immunized and challenged after 2 years, one died. At the end of one year the serum of unchallenged monkeys neutralized the test dose of toxin at a dilution of 1 in 3 or higher. Thereafter the immunity level fell, and after 2 years no antibody was detectable in the serum. In serum obtained after challenge there was a dramatic rise in antibody titre.

Altogether, 1,057 doses of alum-precipitated anthrax antigen were administered subcutaneously to 373 subjects. Reactions were mild but tended to increase in number and duration with successive doses. Circulating antibodies neutralizing the anthrax antigen developed in the immunized subjects. No evidence was found of any relationship between the observed antibody titre and the severity of the reaction, which consisted in pain and tenderness at the site of the injection and, in many cases, erythema. In 2 cases there was generalized urticaria which, however, responded to antihistamines. The authors suggest that these reactions were probably due to the anthrax antigen and not to the culture medium. The antigen can be stored for 2 years or longer without deteriorating. *Kate Maunsell*

Pharmacology

495. **The Relationship between Dosage and Utilization of Orally Administered Iron Compounds**
I. BRADING, E. P. GEORGE, and R. J. WALSH. *Australasian Annals of Medicine* [*Aust. Ann. Med.*] **5**, 118–121, May, 1956 [received Sept., 1956]. 8 refs.

In this paper from the New South Wales Red Cross Blood Transfusion Service, Sydney, and the University of Sydney are described animal experiments on the oral absorption of ferrous and ferric iron.

Radioactive iron (^{59}Fe) was given as ferric chloride in gradually increasing doses to male albino rats through a polyethylene stomach tube. Later the same technique was applied to ^{59}Fe in the form of ferrous sulphate. Three weeks after the iron was administered viviperfusion was performed and the blood removed subjected to assay for radioactivity. The rats were then killed; the liver and spleen were removed, weighed, and digested with sulphuric and perchloric acids and their radioactivity estimated.

The results show a gradual increase in the amount of iron absorbed; 30 times as much was absorbed from a dose of 5·025 mg. as from a dose of 0·025 mg. of ferric iron. The percentage absorption, however, diminished from 38·8% with a dose of 0·025 mg. to 6·4% with a dose of 5·025 mg. Similar results were observed with ^{59}Fe in the ferrous form. It was found that the percentage absorption and the absolute amount absorbed for ferric iron were greater than for ferrous iron at every level of dosage. The dosage of iron per kg. of body weight used in the present study was similar to the usual therapeutic dosage.

The species differences in relative absorption of ferric and ferrous forms of iron are discussed, and it is suggested that there is little reason for administering massive therapeutic doses of iron by mouth.

I. McLean Baird

496. **Coumadin (Warfarin) Sodium, a New Anticoagulant**
J. H. NICHOLSON and T. LEAVITT. *New England Journal of Medicine* [*New Engl. J. Med.*] **255**, 491–501, Sept. 13, 1956. 8 figs., 22 refs.

" Coumadin " (" warfarin ") sodium was used as an anticoagulant in 100 cases of thrombo-embolic disease over a 2-year period at the Lawrence General and Bon Secours Hospitals, Methuen, Massachusetts. Included were 61 cases of myocardial infarction and coronary insufficiency, 15 cases of pulmonary embolism, 3 cases of arterial embolism, 18 cases of acute thrombophlebitis, and 3 cases of rheumatic heart disease. The drug was used both for acute episodes and for prophylaxis. It was initially administered intravenously, but subsequently by mouth; the authors claim that there was no essential difference between these two methods of administration. Blood prothrombin levels, determined by Quick's one-stage method on whole plasma, were estimated initially at 4, 8, and 12 hours, and later at 24-hour intervals, a level of 10 to 35% being regarded as evidence of satisfactory control. Initial dosage (based on 1 mg. per kg. body weight) varied between 37·5 and 81·25 mg.

A satisfactory hypoprothrombinaemia was obtained in 23% of cases within 24 hours, 71% within 36 hours, and 100% within 48 hours. Heparin was used in the early stages only for patients with pulmonary embolism, in doses of 50 to 75 mg. three to four times in the first 24 hours. A persistent effective hypoprothrombinaemia was easily maintained subsequently with relatively predictable doses of coumadin, continuous daily administration being more effective than intermittent dosage at longer intervals. The average daily maintenance dose was 9·6 mg. Clinically, no new pulmonary or arterial embolism and no further thrombophlebitis occurred in any patient under treatment for these conditions.

The only complications produced by the drug were severe haemorrhage in 2 postoperative surgical cases, less severe haemorrhage in one case of peritonitis with a biliary fistula, and excessive hypoprothrombinaemia (prothrombin level below 10%) without any haemorrhage in 3 cases. Both haemorrhage and hypoprothrombinaemia were rapidly controlled with phytonadione (vitamin K_1) in doses of 4 to 50 mg. intravenously. No deaths attributable to coumadin sodium occurred. Control of thrombo-embolism is claimed in 4 cases treated prophylactically for periods varying from 10 to 18 months.

After pointing out the disadvantages of other anticoagulants—dicoumarol, ethyl biscoumacetate, cyclocoumarol, and phenindione—the authors suggest that coumadin sodium meets the criteria of an ideal anticoagulant drug better than any other preparation at present available.

Gerald Sandler

497. **Action of Dibenyline on the Peripheral Circulation**
R. S. DUFF. *British Medical Journal* [*Brit. med. J.*] **2**, 857–860, Oct. 13, 1956. 6 figs., 10 refs.

Phenoxybenzamine hydrochloride (" dibenyline ") is chemically related to dibenamine. In this paper from St. Bartholomew's Hospital, London, an investigation is reported of the effect of dibenyline on diseased blood vessels and of the part played by the sympathetic nerves in the response to the drug in man. The blood flow in 22 sympathectomized limbs was measured by venous occlusion plethysmography. The drug was usually given in the immediate postoperative period, the dose by intravenous infusion being 25 to 60 mg. at a rate of 0·5 to 1 mg. a minute, and by intra-arterial infusion under 0·5 mg. at the rate of 50 to 200 μg. a minute. In sympathectomized limbs without organic narrowing of the vessels dibenyline caused an increase in blood flow, but in similar limbs in which there was organic vascular

disease the drug did not always initiate an increase in flow. Thus dibenyline was capable of increasing the blood flow through vessels which had apparently been deprived surgically of sympathetic innervation. It is pointed out that since dibenyline given intra-arterially acts locally on the vessel into which it is infused, it must be acting on the contractile muscles of the arterioles, for in this investigation it had no effect on the vessels of the opposite limb.

Side-effects tended to occur with intravenous administration in doses of over 40 mg., the most serious being tachycardia and hypotension. The author states that patients should be kept in bed for 24 to 48 hours after intravenous administration. The drug can be given by mouth, but in a dosage greater than 20 mg. a day it may give rise to nasal congestion, lethargy, and giddiness.

G. S. Crockett

498. **Physiological and Morphological Characteristics of the Blocking Action of Aminazine on the Sympathetic Ganglia.** (Физиологическая и морфологическая характеристика блокирующего действия аминазина на симпатический ганглий)

I. P. Anokhina. *Журнал Невропатологии и Психиатрии* [*Zh. Nevropat. Psikhiat.*] **56**, 478–488, 1956. 7 figs., 5 refs.

Writing from the Vishnevskii Surgical Institute, Moscow, the author describes the physiological effects of " aminazine " as observed in experiments on rabbits. In the first group of experiments measurements were made of the changes in the diameter of the pupil resulting from an electrical stimulation of the superior cervical ganglion both before and after the injection of aminazine and adrenaline, singly or in combination. In the second group of experiments the changes in blood pressure resulting from intravenous injections of aminazine and adrenaline were recorded. In addition the cervical sympathetic ganglia were examined histologically.

From the results of these experiments the author concludes that aminazine in doses of 10 to 12 mg. per kg. body weight causes a block in the transmission of impulses through the synapses of the sympathetic ganglia in rabbits; this block is apparently parabiotic in nature and can be reversed by the injection of adrenaline. The actions of aminazine and adrenaline on the blood pressure are directly antagonistic: thus adrenaline injected after aminazine does not cause a rise in blood pressure, while the injection of aminazine during the period of maximal pressor action resulting from a previous injection of adrenaline causes a fall in blood pressure. Histological examination of the cervical sympathetic ganglia removed during the period of action of aminazine showed disappearance of chromaffin elements, but these elements were present in ganglia removed after the effects of aminazine had been annulled by adrenaline. The author suggests that the synaptic block is due to the disappearance of adrenergic substances.

[There is no indication of the chemical structure or of the pharmacological relations or affinities of aminazine. The references to the literature are to work by Russian authors only.] *Marcel Malden*

499. **Effect of Chlorpromazine on Cerebral Hemodynamics and Cerebral Oxygen Metabolism in Man**

J. H. Moyer, G. Morris, R. Pontius, and R. Hershberger. *Circulation* [*Circulation* (*N.Y.*)] **14**, 380–385, Sept., 1956. 4 figs., 7 refs.

In a study of the effect of chlorpromazine on cerebral blood flow, mean blood pressure, and cerebral oxygen metabolism in normotensive subjects carried out at Baylor University College of Medicine, Houston, Texas, 50 mg. of chlorpromazine (" thorazine ") was administered intravenously in 7 cases and intramuscularly in 4, and 2 additional subjects received doses of 25 and 60 mg. respectively intravenously. Pulse and respiratory rates and blood pressure were measured before and repeatedly during each experiment, the cerebral blood flow was measured before and again one hour after the injection, and the arterial blood pressure, blood *p*H and carbon dioxide tension, cerebral oxygen consumption, and cerebral vascular resistance were also determined.

After the intravenous injection of chlorpromazine the cerebral blood flow was reduced from a mean of 48 ml. (range 65 to 37) to a mean of 41 ml. (range 56 to 29) per 100 g. brain tissue per minute, but it is thought the change was probably caused by the associated abrupt reduction in mean arterial blood pressure from 95 mm. Hg to 81 mm. Hg rather than by the direct action of the drug on the cerebral circulation, for when the blood pressure was restored to normotensive levels by the intravenous infusion of noradrenaline the cerebral blood flow returned to normal; nor did chlorpromazine depress the cerebral oxygen consumption directly. In contrast, the muscular injection of chlorpromazine did not reduce the blood pressure significantly and the cerebral blood flow and oxygen consumption were unaltered. The metabolic effect of chlorpromazine thus differs from that of morphine and barbiturates, which depress cerebral oxygen uptake without affecting cerebral blood flow.

J. E. Page

500. **Cutaneous Sensitivity Reactions to Chlorpromazine**

J. F. Mullins, I. M. Cohen, and E. S. Farrington. *Journal of the American Medical Association* [*J. Amer. med. Ass.*] **162**, 946–948, Nov. 3, 1956. 10 refs.

501. **Study on the Effect of Overdoses of Pentylenetetrazol and Barbiturate Combinations in Human Volunteers**

J. F. Fazekas, L. R. Goldbaum, T. Koppanyi, and J. G. Shea. *American Journal of the Medical Sciences* [*Amer. J. med. Sci.*] **231**, 531–541, May, 1956. 1 fig., 18 refs.

The authors have previously reported that a mixture of pentylenetetrazole (leptazol) and pentobarbitone sodium delayed onset of sleep, and that simultaneous administration of three parts of leptazol (in doses up to 6,000 mg.) to one of pentobarbitone sodium (up to 2,000 mg.) gave significant protection against the depressant effects of the latter. They now describe an investigation carried out at Georgetown University School of Medicine, Washington, D.C., to determine the duration

of action and toxicity of such combinations of drugs, and also to assess the " protective " effect of the leptazol.

The tests were performed on healthy male adult volunteers, in whom doses of from 1,300 to 2,000 mg. of pentobarbitone sodium taken simultaneously with three times that amount of leptazol produced no anaesthesia or severe central nervous depression, whereas in a control group 800 to 1,000 mg. of pentobarbitone sodium given alone caused in most cases a marked depression and light anaesthesia. Pentobarbitone sodium administered alone was absorbed more rapidly from the gastrointestinal tract than the mixture, but the rate of disappearance of the drug from the blood, namely, 1·5% of the ingested dose per hour, was the same as when the mixture was given. Similar results were obtained with secobarbital (quinalbarbitone) sodium and its mixture with leptazol.

It is considered that leptazol gives effective protection when taken simultaneously with doses of barbiturates capable of producing coma or even death. In these conditions leptazol did not produce convulsions, and hence in the dosage range tested leptazol and the barbiturates are mutually antagonistic. The mechanism of the action of leptazol is not yet understood, but several hypotheses are discussed. Some of the effects of the drug may persist for up to 24 hours. *L. A. Elson*

502. **The Influence of Hyoscine and Atropine on Apomorphine-induced Vomiting in Man**
B. ISAACS. *Clinical Science* [*Clin. Sci.*] **15**, 177–182, 1956. 2 figs., 8 refs.

503. **Dipipanone Hydrochloride in the Treatment of Severe Pain. A Report of 200 Cases**
R. O. GILLHESPY, E. COPE, and P. O. JONES. *British Medical Journal* [*Brit. med. J.*] **2**, 1094–1096, Nov. 10, 1956. 4 refs.

Dipipanone (DL-6-piperidino-4:4-diphenylheptan-3-one), an analgesic closely related chemically to methadone, was given subcutaneously to two groups of patients at the Dudley Road Hospital, Birmingham: Group 1 contained 100 with pain for which a potent analgesic was necessary; and Group 2 contained 100 who had undergone major gynaecological operations. Patients in Group 1 received 20 mg. of dipipanone 8-hourly until analgesia was no longer required, while patients in Group 2 received 25 mg. of the drug 6-hourly for 48 hours. The initial intensity of the pain was noted, and at intervals up to 8 hours after the drug was given the degree of relief of pain (classified as " complete", " moderate ", " slight ", or *nil*), the degree of hypnosis (" asleep ", " very drowsy ", " slightly drowsy ", or *nil*), and any side-effects were recorded.

Complete relief of pain was obtained by 67 patients in Group 1 and 94 in Group 2, while moderate relief was experienced by 27 and 4 respectively. The onset of analgesia was noted within 10 minutes, and in 20 to 30 minutes analgesia was maximal. In most cases an " adequate level " lasted about 5 hours. Nausea, vomiting, sweating, and giddiness occurred after 4 to 5% of 1,603 injections. In all but one of the patients these side-effects were mild; in the remaining one they were severe enough to necessitate withdrawal of the drug. There was no obvious drowsiness, depression of respiration, constipation, or reaction at the site of injection, and no withdrawal symptoms were noted after as many as 80 effective analgesic doses.

The authors conclude that in the dosage employed dipipanone is an effective analgesic. *T. J. Thomson*

504. **N-Acetyl-*para*-aminophenol as an Analgesic. A Controlled Clinical Trial Using the Method of Sequential Analysis**
D. R. L. NEWTON and J. M. TANNER. *British Medical Journal* [*Brit. med. J.*] **2**, 1096–1099, Nov. 10, 1956. 1 fig., 8 refs.

N-acetyl-*p*-aminophenol (N.A.P.A.P.) is the non-toxic metabolite of acetanilide and phenacetin through which those drugs appear to exert their antipyretic and analgesic action in the human body, and has recently come on to the British market under the trade name of " panadol ".

A controlled clinical trial of the analgesic effect of N.A.P.A.P. compared with that of tab. codein. co. *B.P.* has been carried out in patients suffering from chronic painful rheumatic conditions. Every patient received one drug for a period of a week followed by the other during a second week, and at the end of the fortnight was required to state which drug was the more effective. During the following fortnight a second similar comparison was made. The drugs were given under a randomization scheme which ensured that at no time did either the patient or the doctor know which drug was being taken.

The statistical method known as sequential analysis was used, the principles and advantages of which are described. In the main analysis only patients whose preferences were consistent from one fortnight to the next were plotted. After 42 patients had been tested the analysis terminated with the result that tab. codein. co. 2 tablets three times a day was in general superior to N.A.P.A.P., 1 g. (2 tablets) three times a day. No significant side-effects were noted during the administration of N.A.P.A.P.

The repetition of the test in each patient makes it possible to assess patient–drug interaction—that is, whether there is a significant tendency for particular patients to prefer N.A.P.A.P. even though the majority prefer tab. codein. co. A χ^2 test between the numbers whose preferences were consistent and those who were inconsistent shows that this tendency does in fact exist.

Thus the design of the experiment permits us to state: (1) that tab. codein. co. is a superior analgesic to N.A.P.A.P. in the majority of patients of the sort we tested; and (2) that nevertheless a significant minority of individuals judge that for them N.A.P.A.P. is a better analgesic.—[Authors' summary.]

505. **Analgesic Properties of Mixtures of Chlorpromazine with Morphine and Meperidine**
G. L. JACKSON and D. A. SMITH. *Annals of Internal Medicine* [*Ann. intern. Med.*] **45**, 640–652, Oct., 1956. 8 figs., 15 refs.

Chemotherapy

506. **Studies of the Action of Spiramycin *in vitro* Compared with That of Other Antibiotics.** (Recherches sur l'action de la spiramycine *in vitro* comparée à celle d'autres antibiotiques)
H. GÄRTNER. *Annales de l'Institut Pasteur* [*Ann. Inst. Pasteur*] **91**, 312–322, Sept., 1956. 1 fig., 15 refs.

The sensitivity of 750 strains of 10 species of microorganism to spiramycin (" rovamycin ") has been studied at the Institute of Hygiene and Bacteriology, University of the Saar, and compared with that to three commonly used antibiotics. The sensitivity tests were carried out on sheep-blood agar plates with cavities containing the antibiotics [amount not stated], and in all cases the degree of sensitivity, as denoted by the area of limitation of growth, was compared with the degree observed with the standard Oxford *Staphylococcus aureus* SG 511. The results of the sensitivity tests on the various organisms are given in graphic form.

Of 86 strains of haemolytic streptococcus and *Streptococcus salivarius* examined, none was found to be resistant and only 7 strains were less sensitive than the Oxford staphylococcus. Of 133 strains of *Staphylococcus aureus*, only 2 strains were completely resistant and 34 strains less sensitive than the Oxford staphylococcus. Results with enterococci were less favourable, for of 125 strains examined, 68 were less sensitive than the standard staphylococcus. The Gram-negative bacilli showed much greater resistance, the majority of the strains being less sensitive than the Oxford staphylococcus and increasing numbers of completely resistant strains being encountered, particularly among the *Pseudomonas* and *Proteus* groups. Lastly, the examination of 60 strains of *Staphylococcus aureus* by a dilution method showed that 32 of these strains were sensitive to concentrations of between 2·5 and 5 μg. per ml. (the Oxford staphylococcus being sensitive to 5 μg. per ml.), while 14 strains were sensitive only to a concentration of 10 μg. per ml.; the remaining 14 strains were very resistant, being inhibited only at 100 to 1,000 μg. per ml. The author compares these figures obtained *in vitro* with blood levels of spiramycin *in vivo* reported by other workers, which ranged from 1·6 to 8 μg. per ml. according to the dose given.

The author then compared the sensitivity of the same organisms to spiramycin with that to penicillin, aureomycin, and streptomycin. The results, which are tabulated, show that in the case of haemolytic streptococci the sensitivities to all four antibiotics were practically the same. In the case of *Streptococcus salivarius* 46 out of 72 sensitive strains reacted equally to all antibiotics, in 10 instances spiramycin was more active than the others, and in 2 instances less efficient; for 14 strains the results with the antibiotics were not uniform and this group is further analysed (as it is in all the tables). Of 133 strains of *Staphylococcus aureus*, only 4 were more sensitive to the other antibiotics than to spiramycin, 30 reacted equally, in 38 cases spiramycin was more active, and for 61 strains the results were variable. Of 123 strains of enterococci, 37 were more, 32 equally, and 2 less sensitive to spiramycin, 52 strains giving variable results, while of 250 strains of *Escherichia coli*, spiramycin was more effective against 32, equally effective against 23, and less effective against 6, 189 giving variable results. All the strains giving variable results are analysed in detail, showing which antibiotic gave the best result with individual strains as compared with the action of spiramycin.

The author concludes that spiramycin is one of the most effective antibiotics against haemolytic streptococci and *Strep. salivarius*, and although in the case of enterococci and staphylococci the results obtained were less uniform, they were in general satisfactory. In regard to *Esch. coli*, however, the results varied very widely, so that some infections may respond dramatically whereas others may not. He suggests that in acute infections immediate treatment with spiramycin is justified when cocci are suspected as the infecting organisms. It has the advantage over other chemotherapeutic agents in being effective by mouth. However, in meningeal infections spiramycin is less effective as its passage through the meningeal barrier is relatively poor.

R. F. Jennison

507. **Palliation of Carcinomatosis with Ascites by Means of Hemisulfur Mustard (2-Chloro-2′-hydroxydiethyl Sulfide)**
A. M. RUTENBURG and A. M. SELIGMAN. *New England Journal of Medicine* [*New Engl. J. Med.*] **255**, 361–368, Aug. 23, 1956. 4 figs., 1 ref.

At the Beth Israel Hospital, Boston, and the Sinai Hospital, Baltimore, 30 patients with advanced carcinoma were treated with hemisulphur mustard (2-chloro-2′-hydroxydiethyl sulphide), which is poorly soluble in water, is supplied in solution in ether, and must be stored at temperatures of $-10°$ to $-20°$ C. until just before use. Doses of 100 to 400 mg. diluted in 50 ml. of saline were given through a catheter in the brachial vein or superior vena cava, the catheter being left in position until up to 4 doses had been given at 2- to 4-day intervals.

Toxic effects included nausea, vomiting, tremor, convulsions (2 cases), and vascular collapse. In all cases the disease was far advanced and either inoperable or resistant to irradiation. Subjective and objective improvement was noted in 14 patients, in 3 of whom there was striking palliation for 8 to 28 months. Temporary improvement lasting about 3 months was obtained in 11 cases. Patients with ovarian carcinoma tended to respond particularly well, there being general palliation, with reduction in ascites and in the size of the tumour mass, in 9 out of 14 such cases.

The paper includes 9 case reports and reproductions of photomicrographs of histological sections before and after treatment.

Kenneth Gurling

Infectious Diseases

508. **The Transmission of *Staphylococcus aureus***
R. HARE and C. G. A. THOMAS. *British Medical Journal* [*Brit. med. J.*] **2**, 840–844, Oct. 13, 1956. 10 refs.

The authors have investigated at St. Thomas's Hospital, London, the mechanism by which *Staphylococcus aureus* is transmitted from carriers to other persons. Little evidence for the carriage of the organism on airborne droplets from the anterior nares was found, but large numbers of *Staph. aureus* were isolated from the skin, clothing, and bedding of nasal carriers. Far fewer organisms were found on the skin, clothes, and other belongings of subjects not harbouring *Staph. aureus* in the nose.

Further studies showed that rubbing the skin or the hair, washing the hands, and other types of activity liberated large numbers of *Staph. aureus* into the air. The authors suggest that air currents carry *Staph. aureus* released in this way from carriers to normal persons, either producing in the recipients the nasal carrier state or causing lesions in susceptible tissues. It was also shown that some carriers contaminated the atmosphere in their vicinity with *Staph. aureus* particularly when exercising, even although wearing a complete set of sterile operating clothes. Hospital patients suffering from mild staphylococcal sepsis did not carry a greatly increased number of *Staph. aureus* on their skin and clothing as compared with patients free from such lesions. The chief culprit therefore seems to be the nasal carrier.

[Although the application of these results to the prevention of staphylococcal infection was considered to be outside the scope of the study, this paper is nevertheless of importance to all concerned with cross-infection in hospitals.] *B. Ruebner*

VIRUS DISEASES

509. **A Study of the Role of Adenoviruses in Acute Respiratory Infections in a Navy Recruit Population**
W. P. ROWE, J. R. SEAL, R. J. HUEBNER, J. E. WHITESIDE, R. L. WOOLRIDGE, and H. C. TURNER. *American Journal of Hygiene* [*Amer. J. Hyg.*] **64**, 211–219, Sept., 1956. 21 refs.

A study is reported of the part played by adenoviruses in acute respiratory infections occurring during the first three months of 1954 among 769 recruits at a U.S. naval training centre. The subjects examined included some with and some without evidence of streptococcal or influenzal infection, and some suffering from non-respiratory complaints, these last providing a control group for the series. In each case in addition to routine physical examination a chest radiograph was obtained, the differential leucocyte count was determined, and throat swabs were cultured. Nasal washings and a blood specimen were taken at the initial examination, and a further specimen of blood was taken 3 to 5 weeks later. The nasal washings were tested for the presence of adenoviruses in HeLa-cell cultures, and the titres of complement-fixing and neutralizing antibodies to adenovirus Type 4 (RI-67 strain) in the two specimens of blood were compared.

In 29 cases of febrile upper respiratory infections with no evidence of streptococcal or influenza-virus infection Type-4 adenovirus was isolated; this was accompanied by a significant increase in complement-fixing antibody titres. In this group the clinical findings, in order of frequency, were sore throat, malaise, fever, rhinitis, cough, hoarseness, headache, nasal congestion, coryza, and pharyngitis. Pneumonia and conjunctivitis each occurred once in this group. In 9 cases evidence of adenovirus infection was associated with streptococcal or influenza-virus infection. Although adenovirus was not isolated from any of the patients with non-respiratory disease, there was a rise in complement-fixing antibody titre in about 4% of these cases.

In conclusion the authors state that Type-4 adenovirus was recovered exclusively from subjects with acute respiratory illness and that it was recovered only during the first 5 days of the infection. It was isolated four times more frequently in febrile than in afebrile conditions. In approximately one-fifth of all cases of non-streptococcal, non-influenzal febrile upper respiratory infection there was laboratory evidence of infection with Type-4 adenovirus. *D. Geraint James*

510. **Studies on Acute Respiratory Illness in Naval Recruits, with Emphasis on the Adenoviruses (APC-RI)**
R. L. WOOLRIDGE, J. T. GRAYSTON, J. E. WHITESIDE, C. G. LOOSLI, M. FRIEDMAN, and W. E. PIERCE. *Journal of Infectious Diseases* [*J. infect. Dis.*] **99**, 182–187, Sept.–Oct., 1956. 1 fig., 16 refs.

511. **Clinical and Laboratory Studies in Patients with Respiratory Disease Caused by Adenoviruses (RI-APC-ARD Agents)**
H. E. DASCOMB and M. R. HILLEMAN. *American Journal of Medicine* [*Amer. J. Med.*] **21**, 161–174, Aug., 1956. 11 figs., 31 refs.

The authors report, from the Walter Reed Army Institute of Research, Washington, D.C., the clinical and laboratory findings in 45 U.S. Army recruits aged 18 to 23 who were admitted to hospital with acute respiratory illness in January, 1954, at which time an epidemic of respiratory disease was in the rising phase. During their 3 weeks in the Army all the patients had suffered from minor respiratory symptoms upon which the acute respiratory illness requiring admission to hospital was superimposed. The basic syndrome of fever, pharyngitis, and cough was associated with one or more of the following: conjunctivitis, rhinitis, catarrhal otitis media

or externa, laryngitis, tracheobronchitis, bronchiolitis, pneumonitis, and constitutional symptoms. Details of representative cases are given and radiographs of a patient with pneumonitis and atelectasis are reproduced.

Just before admission to hospital throat washings were collected and tested for the presence of the adenoidal-pharyngeal-conjunctival (A.P.C.) group of viruses (adenoviruses) by inoculation of HeLa-cell cultures. The strains isolated were typed with monotypic rabbit antisera. Blood samples were taken on admission and again 2 and 4 weeks later; the sera were tested for complement fixation with antigen of the RI-67 strain of virus. Some sera were subjected to neutralization tests in HeLa-cell cultures using Type-4 virus (RI-67), Type-7 virus (Strain RI-4-202, isolated during the study), and, in some instances, the particular virus strain isolated from the patient. Throat washings from 11 of the 45 patients yielded adenoviruses, and each of the isolates was identified as belonging to Type 7. All patients showed a diagnostic rise in complement-fixing antibody, the increase in 32 cases ranging from 16-fold to 64-fold. The sera from 12 patients tested for neutralizing antibody showed a significant rise in titre against Type-7 virus, and in 8 instances against Type-4 virus also. Culture of throat swabs failed to reveal a primary bacterial aetiology, and tests for antibodies against influenza viruses A, B, and C and for a rise in the cold or streptococcus-MG agglutinins gave negative results.

Joyce Wright

512. **Infection of Volunteers by a Virus (A.P.C. Type 1) Isolated from Human Adenoid Tissue**

A. T. RODEN, H. G. PEREIRA, and D. M. CHAPRONIERE. *Lancet* [*Lancet*] **2**, 592–596, Sept. 22, 1956. 1 fig., 9 refs.

The cultivation *in vitro* of human adenoid tissue has led to the isolation of a group of viruses (now generally referred to as adenoviruses) in which at least 8 different serological types have been differentiated. While certain types, notably Types 3 and 4, are considered to be the causes of the syndromes of " acute respiratory disease " and " pharyngo-conjunctival fever ", the relation of the other types to human disease is not yet clearly established.

A strain (ADS 17) of Type-1 adenovirus, isolated from the surgically removed adenoids of a child, was given intranasally to 11 volunteers at the Common Cold Research Unit, Salisbury, Wiltshire. The infective material was the fluid phase from a first passage of Strain ADS 17 in cultures of human embryonic kidney tissue. Of the 11 volunteers, 6 remained well, 3 developed trivial symptoms (nasal stuffiness and slight sore throat), and 2 developed clinical evidence of an upper respiratory-tract infection; in both these patients there was an incubation period of 4 or 5 days before the onset of sore throat and cervical adenitis. In one patient the temperature rose to 101° F. (38·3° C.) on 2 consecutive days, while in the other, who remained afebrile, unilateral nasal obstruction was present for 2 or 3 days. No virus was isolated from any of the subjects on the second day after inoculation, but Type-1 virus was isolated from 4 individuals, including the 2 who were ill, by the 6th day. Samples of serum collected before inoculation from these 4 individuals showed neutralizing-antibody titres of less than 1 in 20 against Type-1 virus, whereas the remaining subjects, from whom no virus was isolated, possessed high neutralizing-antibody titres against this virus before the intranasal inoculation. A definite rise in titre against Type-1 virus occurred in 7 of the 11 volunteers, and increases in titre against various heterologous types also occurred. However, the level of complement-fixing antibody titre rose only in those from whom the virus was isolated, and these rises were not type-specific.

J. E. M. Whitehead

513. **Incidence of Previous Type-II Infection in Patients with Type-I Paralytic Poliomyelitis**

D. M. S. DANE and E. M. BRIGGS. *Lancet* [*Lancet*] **2**, 851–853, Oct. 27, 1956. 5 refs.

The study reported in this paper from the Queen's University of Belfast was aimed at finding out whether possession of antibody to Type-II poliomyelitis virus gave protection against paralytic disease in an infection with Type-I virus. It was found that among 26 cases of paralytic poliomyelitis occurring in Northern Ireland between October, 1955, and March, 1956, from which Type-I virus had been isolated, only one had antibody against Type-II virus in a titre of more than 1 in 64 in both the acute and the convalescent stages. Low titres of Type-II antibody were detected in the acute stage in 6 others, but not in the convalescent stage. All had antibody against the homologous infecting type of virus and 5 out of 6 had stationary high titres of Type-III antibody. From the results of a recent survey of poliomyelitis antibodies among children in Northern Ireland (*Lancet*, 1956, **1**, 481) it was calculated that 50% of these patients might have been expected to have had Type-II antibody as a result of previous Type-II infection. This study, together with other evidence, suggests that there may be some cross-protection against paralytic poliomyelitis between the Type-I and Type-II viruses. Vaccination with an attenuated Type-II virus might not only protect against Type-II paralytic disease, but also give some measure of protection against a paralytic attack caused by the other two types without affecting their endemic status.

A. Ackroyd

514. **Clinical Features of Aseptic Meningitis Caused by Coxsackie-B Virus**

D. L. MCLEOD, A. J. BEALE, G. A. MCNAUGHTON, and A. J. RHODES. *Lancet* [*Lancet*] **2**, 701–703, Oct. 6, 1956. 13 refs.

The syndrome of aseptic meningitis may be due to infection by a variety of agents. Among viruses that have been implicated are the poliomyelitis, Coxsackie-B, lymphocytic choriomeningitis, mumps, and herpes simplex viruses, and recently certain " orphan " viruses.

In the present paper are reviewed the clinical and laboratory findings in 17 cases of aseptic meningitis admitted to the Hospital for Sick Children, Toronto, between 1950 and 1955, in which Coxsackie-B virus was the causal agent. All the cases occurred in the

summer and early autumn and formed part of a series of 96 cases diagnosed as of "non-paralytic poliomyelitis" which were studied virologically and in 18 of which poliomyelitis virus was demonstrated. Most of the patients infected with Coxsackie-B virus had clinical signs of meningitis, nausea, vomiting, and headache. Pain in the neck and back occurred frequently, and there was myalgia in about one-third of the cases. Pleurodynia did not occur. There was no muscular tremor or alteration of the reflexes such as is found in the preparalytic phase in cases of poliomyelitis in which paralysis subsequently develops. The average cerebrospinal-fluid cell count was 171 per c.mm., with a range of 15 to 700 per c.mm. Lymphocytes were the predominant cells in 50% of the cases.

The authors conclude that whereas in mumps, herpes simplex, and lymphocytic choriomeningitis infections of the nervous system there is sometimes a significant feature in the history or clinical findings which may indicate the aetiological agent responsible, in aseptic meningitis due to poliomyelitis or Coxsackie-B virus or to "orphan" viruses there is nothing in the clinical findings to suggest which is the infecting virus.

J. E. M. Whitehead

515. **Treatment of Measles Encephalitis with Corticotrophin**

E. Appelbaum and C. Abler. *A.M.A. Journal of Diseases of Children* [*A.M.A. J. Dis. Child.*] **92**, 147–151, Aug., 1956. 6 refs.

The authors describe the treatment with ACTH (corticotrophin) of 17 patients with measles encephalitis admitted to the Willard Parker Hospital, New York, during the period 1952–5. The main presenting features were high temperature, convulsions (in 14 cases), coma (in 10), and signs of meningeal irritation. [No description of the rash or its relation to the onset of cerebral symptoms is given.] The cerebrospinal fluid was examined in 16 cases, a lymphocytic pleocytosis being present in 13 cases and an increased protein content in 10. In most instances the initial administration of ACTH was intravenous, but the intramuscular route was also employed. [No precise information is given on this point.] In 11 cases treatment was begun on the day of onset of cerebral signs, whereas in the other 6 it was delayed 3 to 6 days. The daily dose varied from 5 to 80 mg. (average 25 mg.), and the total dose varied from 25 mg. (one dose) to 320 mg.

Remission of fever and improvement in the mental state occurred within 1 to 4 days of starting treatment in 11 cases and within 6 to 13 days in 6 others. Complications occurred in 4 cases, and included impairment of vision, aphasia, recurrent convulsions, and difficulty in focusing. There were no deaths, but 3 patients showed residual stigmata, including impaired vision, aphasia, euphoria, and mental retardation, on discharge. [The length of stay is not stated.] Of 16 patients who were followed up for periods varying from 7 months to $3\frac{3}{4}$ years, 15 had no residual sequelae, but one suffered from mental retardation and impaired speech $3\frac{1}{2}$ years after discharge.

The authors speculate on the mode of action of ACTH, and suggest that although the series is too small to permit definite conclusions to be drawn, the favourable results obtained in all but one case indicate that ACTH may have a beneficial effect in measles encephalitis.

[It is difficult to share the authors' enthusiasm for ACTH as measles encephalitis is a condition which is self-limiting and whose outcome is difficult to foretell. The paucity of details and the absence of controls makes evaluation of their findings impossible.]

I. M. Librach

SARCOIDOSIS

516. **Diagnosis and Treatment of Sarcoidosis**

D. G. James. *British Medical Journal* [*Brit. med. J.*] **2**, 900–904, Oct. 20, 1956. 27 refs.

In this paper, based on the study of 150 cases of histologically proven sarcoidosis seen at the Middlesex Hospital, London, the author discusses the diagnosis and treatment of this protean disorder. Clinically, it presented most frequently in the form of intrathoracic involvement, which was discovered either when abnormalities were found on routine chest radiography in an apparently healthy young adult or because of a complaint of breathlessness. Skin lesions developed in 67 (45%) of the patients, and ophthalmic changes in 42 (28%). At some stage of the disease there were enlarged lymph nodes in 56 cases (37%) and a palpable spleen in 27 (18%). In the ancillary investigations a normal chest radiograph was observed in only 14 patients (8%), all the others presenting some abnormality. Radiography of the hands and feet on the other hand was unhelpful, abnormalities being found in only 8 instances (5%). The Mantoux reaction to 100 T.U. was negative in two-thirds of the cases, but when 5 T.U. in an oily delaying vehicle was injected intradermally a positive response was obtained in two-thirds of these negative reactors. In 14 out of 50 cases electrophoretic analysis of the serum proteins showed a rise in the serum globulin fraction. The serum calcium level was raised in only one case.

Histological evidence of sarcoidosis was obtained from a wide variety of tissues, including the skin, lymph nodes, liver, lung, bronchus, conjunctiva, and nasal mucosa. The Kveim reaction was positive in 83 (75%) of the 110 cases in which it was performed; the beryllium skin-patch test for berylliosis—which may closely resemble sarcoidosis—was negative in all of the 30 patients tested.

Antituberculous drugs were tried in 31 cases, but were considered not to have influenced the course of the disease. The oral administration of cortisone to 20 patients, who were followed up for more than one year, resulted in the early lesions being well controlled, but results in the chronic fibrotic stage were disappointing. Although the steroid hormones are the most useful line of therapy in this relatively benign condition, it is recommended that they be employed only when specifically indicated. Sanatorium treatment is not necessary and may even be harmful. *John Fry*

Tuberculosis

517. **Freeze-dried B.C.G. Vaccination of Newborn Infants with a British Vaccine**
M. I. GRIFFITHS and W. GAISFORD. *British Medical Journal* [*Brit. med. J.*] **2**, 565–568, Sept. 8, 1956. 3 refs.

In this paper from St. Mary's Hospital and the University, Manchester, an investigation is reported into the minimum dosage of a British freeze-dried B.C.G. vaccine necessary to produce a result comparable with that obtained with the Danish liquid vaccine. It was found that a vaccine containing 110,000 to 130,000 viable organisms per inoculating dose was only slightly less antigenic than the Danish vaccine, and up to the time of the report it had not caused any complications. This dosage is therefore regarded as the optimum. The authors state in conclusion that since accuracy of bacillary dosage is now a practical possibility, it is probable that liquid vaccines will be replaced by freeze-dried preparations, which have none of the disadvantages of the former. *John M. Talbot*

518. **The Effects of Isoniazid Treatment on the Tuberculin Reaction and on the Healing of BCG Vaccine-induced Ulcers**
J. D. ARONSON, H. C. TAYLOR, and D. L. KIRK. *American Review of Tuberculosis and Pulmonary Diseases* [*Amer. Rev. Tuberc.*] **74**, 7–14, July, 1956. 11 refs.

The effect of treatment with isoniazid on the tuberculin reaction and on the healing of ulcers following BCG vaccination in two groups of persons was studied. One group of 116 persons received their initial vaccination while the second group of 122 persons represented those who had been vaccinated from one to five times previously with BCG vaccine and who were again injected with BCG vaccine at the same time as the first group.

Six weeks after vaccination a significantly higher percentage of those who had received their initial vaccination reacted to 0·01 mg. of OT than did those who had previously received repeated injections of BCG vaccine. Beginning 47 days after vaccination, approximately one half of those who had received an initial vaccination and one half who had received repeated vaccinations were given 5 mg. of isoniazid per kg. of body weight daily for 64 days, while the remaining half of each group served as controls. Of those who had received their initial vaccination 111 days previously, a somewhat smaller but comparable percentage of both isoniazid-treated and control subjects reacted to 0·01 mg. of OT and to 0·1 mg. of OT than reacted 42 days after vaccination. Among those who had previously received repeated vaccinations a larger but not statistically significant percentage of those treated with isoniazid failed to react to 0·01 mg. of OT after treatment than before treatment, while the percentage of control subjects who reacted to this dose of OT remained the same. The percentage who reacted to 0·1 mg. of OT, 42 and 111 days after vaccination, was approximately the same in both groups,

The character and rate of healing of the BCG-induced ulcers were not significantly different in the isoniazid-treated group when compared with the control group.—[From the authors' summary.]

519. **The Management of Spontaneous Pneumothorax Complicating Pulmonary Tuberculosis**
K. REEMTSMA, R. H. CLAUSS, and R. H. WYLIE. *American Review of Tuberculosis and Pulmonary Diseases* [*Amer. Rev. Tuberc.*] **74**, 351–357, Sept., 1956. 11 refs.

Experience in the management of 20 cases of spontaneous pneumothorax complicating pulmonary tuberculosis, seen at Bellevue Hospital, New York, between 1950 and 1954, is described. The ages of the patients, 18 males and 2 females, ranged from 23 to 69 years. In all cases the diagnosis of tuberculosis was confirmed by isolation of acid-fast bacilli from sputum or gastric washings. Of the 20 patients, 4 had pneumothorax only, 7 hydropneumothorax, 5 tuberculous pyopneumothorax, and 4 mixed pyopneumothorax.

Chemotherapy included administration of PAS with streptomycin or isoniazid and penicillin, broad-spectrum antibiotics being added later or substituted for penicillin as determined by the clinical course or the results of drug-sensitivity tests. Underwater seal drainage through an intercostal No. 24 French two-hole catheter was instituted in all cases, suction being employed in recent cases. In the presence of fluid the catheter was introduced at a dependent site; in the absence of fluid it was introduced into the second intercostal space anteriorly, a 14-gauge thin-walled needle, through which a plastic tube was passed, being used. Drainage was stopped only when expansion seemed assured or there was no longer evidence of empyema.

There were no deaths in the series. In 14 cases the response was satisfactory, no surgical procedure other than intercostal drainage being required. In the remaining 6 cases various operations were necessary—namely, thoracoplasty, thoracoplasty followed by pneumonectomy, pneumonectomy with concomitant thoracoplasty, segmental resection, and decortication. Factors favouring a successful outcome of intercostal drainage were: (1) a short interval between the onset of pneumothorax and insertion of the tube (12 out of 16 patients treated within 2 weeks of onset had permanent re-expansion); and (2) prompt re-expansion following insertion of the tube (10 out of 12 patients whose lungs re-expanded within a week required no further treatment). In 4 cases a second or third tube thoracotomy had to be carried out for recurrent pneumothorax, but the end-results in all were good, no further surgery being necessary.

The low mortality in this series is attributed to the use of antituberculous drugs. The authors suggest that if thoracotomy with suction fails after 6 to 8 weeks more extensive procedures—decortication, resection, or thoracoplasty—should be considered. *Denis Abelson*

Venereal Diseases

520. **Prostitution and Venereal Diseases in Manchester**
S. M. LAIRD. *British Journal of Venereal Diseases* [*Brit. J. vener. Dis.*] **32**, 181–183, Sept., 1956. 4 refs.

The significance of prostitution in relation to the spread of venereal disease was studied among males attending St. Luke's Clinic and the V.D. Clinic of the Royal Infirmary, Manchester, over a period of one year. Altogether 1,257 of the men had gonorrhoea, 376 (30%) as a result of exposure with a prostitute; 592 had non-gonococcal urethritis, 137 (23%) after exposure with a prostitute; and 1,476 had other conditions, excluding syphilis, 219 (29%) after exposure with a prostitute, 144 of this last group requiring treatment.

The author emphasizes the difficulty of securing the attendance at a V.D. clinic of the sexual partner of an infected man when this partner is a prostitute; the personal information necessary for contact tracing is rarely available. There is no doubt that the prostitute contributes substantially to the reservoir of women with untreated gonorrhoea and that treatment of the infected prostitute would be of value in the control of the disease. The author refers to the unsatisfactory state of the law and the system of monetary fines, and considers it would be helpful if Magistrates were to advise prostitutes to attend V.D. clinics for examination and treatment when necessary, perhaps at a special session of such clinics. He expresses the hope that " the Report of the Departmental Committee which is at present considering the law and practice relating to homosexuality and prostitution will include recommendations on this aspect of the problem of prostitution, and that realistic legislation will permit police and Magistrates to discourage prostitution and assist in the control of venereal disease ".

V. E. Lloyd

521. **Granuloma Inguinale (Venereum)**
G. H. KNIGHT and W. FOWLER. *British Medical Journal* [*Brit. med. J.*] **2**, 980–981, Oct. 27, 1956. 3 figs., 7 refs.

The authors report, from the General Hospital, Birmingham, 8 cases of granuloma inguinale occurring in 7 male patients from the West Indies and in one from East Pakistan. In every case the diagnosis was established by demonstrating Donovan bodies in the cytoplasm of the larger monocytes. Of 6 of the patients who stated that they had had no sexual intercourse since leaving their own country, 3 West Indians and the Pakistani first noticed the lesion during the voyage to Britain; in 2 it developed 3 and 4 weeks respectively after arrival in England, thus making the possible period of incubation in these cases 15 to 84 days; the other 2 patients had been in this country for over 2 years and admitted exposure.

Of 4 patients treated with streptomycin (1 g. daily), one defaulted before healing was complete, 2 treated for 9 and 14 days respectively defaulted 2 weeks after the lesion had healed, while in the 4th case, which was treated for 3 weeks, the lesion remained healed after 4 months. Of 4 patients treated with oxytetracycline (2 g. daily), one defaulted before healing was complete, one given a 3-week course defaulted a week after healing had occurred, but 2 who continued treatment for 4 weeks remained well during an observation period of 2 months.

R. R. Willcox

522. **The Use of Sitolipin Antigen in the Kolmer Wassermann Reaction and Slide Precipitation Test.** (Das Luesantigen Sitolipin in der Kolmertechnik und im Mikrotest)
F. FEGELER. *Zeitschrift für Haut- und Geschlechtskrankheiten* [*Z. Haut- u. GeschlKr.*] **21**, 239–243, Nov. 1, 1956. 3 figs., 5 refs.

At the Westphalia–Wilhelms University Skin Clinic, Münster, 1,000 sera were tested for syphilis with cardiolipin, with calf-heart extract, and with " sitolipin " as antigen by the Wassermann technique and the Kolmer modification of it. Sitolipin, which is obtained from wheat germ, was found to be similar in sensitivity to the other two antigens in the original Wassermann test. With the Kolmer technique, both sitolipin and cardiolipin were about one-third more sensitive than the usual calf-heart antigen and were superior to flocculation reactions. The slide test, which is described, is simple, quick, and comparatively cheap, and proved equally useful whether cardiolipin or sitolipin was used as antigen.

G. W. Csonka

523. **The Influence of Prednisone on the Syphilitic Herxheimer Reaction.** (L'influenza del prednisone sulla reazione di Herxheimer della sifilide)
M. DEPAOLI. *Minerva dermatologica* [*Minerva derm. (Torino)*] **31**, 263–267, Sept., 1956. 30 refs.

After a brief survey of the literature on the use of cortisone in the treatment of syphilis and of the Herxheimer reaction to penicillin the author, writing from the University Dermatology Clinic, Turin, discusses the use of prednisone for the latter purpose. He considers that because of its fewer side-effects prednisone is preferable to cortisone.

To 8 patients with a primary chancre of at least 15 days' duration and to 9 with a florid secondary eruption 5 mg. of prednisone was given 4- or 5-hourly to a total of 3 to 5 doses, beginning usually 4 hours before the first administration of penicillin. As a control, 10 patients with a primary lesion and 3 with diffuse skin lesions were given 300,000 units of penicillin only.

All the control patients showed a rise of temperature to 38·5° to 40·2° C. between 4 and 6 hours after injection, and in 2 of the primary and 3 of the secondary cases there was also aggravation of the clinical picture. In the prednisone-treated group, in all the primary cases

a positive smear was obtained and both primary and secondary cases gave a clear-cut, strongly positive serological reaction. In 7 primary cases and 4 cases with a syphilide (usually roseolo-papular or roseolar) a Herxheimer reaction was completely prevented; in one case of each group the reaction was greatly diminished, and in one secondary case it lasted 14 hours only; in only 3 secondary cases which had been treated with 15 mg. of prednisone was there no benefit. Thus a high percentage of favourable results was obtained.

The author discusses the mode of action of cortisone and cortisone-like hormones; he considers that the beneficial effect is due to the suppression of a hypersensitivity reaction and that these drugs are of great practical value. *F. Hillman*

524. **Jarisch–Herxheimer Reaction following Penicillin Treatment of Early Congenital Syphilis**
A. HOLZEL. *British Journal of Venereal Diseases* [*Brit. J. vener. Dis.*] **32**, 175–180, Sept., 1956. 5 figs., 18 refs.

Between January, 1948, and December, 1952, 80 children with congenital syphilis were treated at three hospitals in Manchester, and in this paper the results obtained in 45, all of whom were under one year of age and were treated exclusively with penicillin, are described. Of these 45 patients, 19 died—14 in the age group 0 to 3 months and 5 in age group 3 to 12 months—a Jarisch–Herxheimer reaction to penicillin being considered a contributory factor in 10. Full details of the lesions, the treatment, and the type of reaction in 4 cases and the post-mortem findings in 3 are given.

There appeared to be two types of fatal reaction. In 3 cases sudden pyrexia, abdominal distension, respiratory distress, and vomiting preceded a fatal syncopal attack within 24 hours of admission. In one case a premature infant had been given 5,000 units of penicillin, intramuscularly, followed by 10,000 units every 4 hours. The second type of fatal reaction, occurring in 7 infants, was less fulminating. The pyrexia which followed the initial penicillin injection receded in the course of 24 hours, but the general condition and weight of the infants deteriorated. Abdominal distension, jaundice, and oedema ensued, and death occurred towards the end of the first week from sudden peripheral circulatory failure. At necropsy in 3 cases the enlarged liver showed marked necrosis.

The author discusses the intensity of syphilis in infants, and draws attention to the marked involvement of the liver and spleen. He considers that the additional stress of the Jarisch–Herxheimer reaction may well have led to complete hepatic failure. In the 10 fatal cases the dosage of penicillin had ranged from 1,000 to 200,000 units per lb. (2,200 to 440,000 per kg.) body weight, and this seems to support the view that the reaction in these cases is an " all or none " type of response.
V. E. Lloyd

525. **Serologic Survey for Syphilis in Migratory Labor Camps of Upstate New York**
E. W. THOMAS and J. GIORDANO. *Public Health Reports* [*Publ. Hlth Rep. (Wash.)*] **71**, 1089–1092, Nov., 1956.

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526. **Clinical Evaluation of a New Triple Penicillin Salt in the Treatment of Acute Gonorrhoea**
G. W. SLEATH and A. J. NELSON. *Canadian Journal of Public Health* [*Canad. J. publ. Hlth*] **47**, 383–387, Sept., 1956. 8 refs.

Two preparations of penicillin, PAM (procaine benzylpenicillin in oil with 2% aluminium monostearate) and BAP (600,000 units of benzathine benzylpenicillin with 300,000 units of procaine benzylpenicillin and 300,000 units of potassium benzylpenicillin made up to 1 ml.), were tried at the Venereal Disease Clinic, Vancouver, in the treatment of 470 bacteriologically proved cases of gonorrhoea and the results compared. Each preparation was given in a single injection of 1·2 mega units, this being considered adequate for curing the gonorrhoea and preventing the development of simultaneously-acquired syphilis.

In the 278 patients who reported back for at least one examination no significant difference was observed between the cure rate with PAM and the cure rate with BAP in males or females (average 97% cure). Fairly severe local reactions occurred at the site of the injection, however, in 55% of patients treated with BAP, and it is therefore concluded that for routine use PAM is to be preferred. *A. J. Gill*

527. **Treatment of Gonorrhoea with Syntomycin.**
(Лечение больных гонореей синтомицином)
O. I. NYUNIKOVA. *Советская Медицина* [*Sovetsk. Med.*] 36–39, No. 7, July, 1956.

At the Central Dermatological and Venereological Institute, Moscow, " syntomycin " was used in the treatment of 146 patients with gonorrhoea, of whom 72 were men, 50 women, and 24 were female children. In 104 cases there had been no previous treatment and 18 had been unsuccessfully treated with penicillin, streptomycin, and sulphonamides. The total dose of syntomycin for adults with acute uncomplicated infection was 10 g.; for those with complications it was 12 to 15 g. spread over a period of 3 or 4 days. Children received 0·02 g. per kg. body weight six times a day for 3 or 4 days.

Gonococci disappeared from the urethral smears after 4 to 9 hours, and from cultures after 6 to 8 hours, depending on the size of the initial dose (which varied from 3 to 4 g. for adults). The urethral discharge usually disappeared later, between 2 and 10 days after the beginning of the treatment. In 6 cases local medication was necessary to stop the inflammatory reaction. Recurrences took place in 3·2% of uncomplicated cases. The patients were followed up for one to 3 months.

Syntomycin is said to appear in the blood 30 minutes after a single oral dose of 0·5 to 1 g., and reaches its maximum concentration (about 75 μg. per ml.) 3 hours after ingestion, but therapeutic concentrations are still present in the blood 6 to 12 hours after such a dose. The drug appears in the urine one hour after a similar dose, reaching a maximum level (about 225 μg. per ml.) after 6 hours, and excretion of the drug ceases in about 14 hours. Therapeutic levels in the blood, after a course totalling 10 g., are maintained for at least 24 hours.
A. Swan

Tropical Medicine

528. **Amino-acids and Kwashiorkor**
J. D. L. HANSEN, E. E. HOWE, and J. F. BROCK. *Lancet* [*Lancet*] **2**, 911–913, Nov. 3, 1956. 1 fig., 9 refs.

Kwashiorkor is a major problem in many underdeveloped countries. As it may not always be practicable to import protein-supplying foods such as milk, an alternative source of good-quality protein must be found.

In a study reported from Groote Schuur Hospital and the University of Cape Town, which was designed to determine the essential limiting nutrients, 37 children with kwashiorkor were given diets containing a mixture of either 18 or 11 synthetic amino-acids, with or without additional vitamins, the 8 essential amino-acids being included in both regimens; the average daily intake was considerably greater than the estimated minimum needs of healthy adults. The criterion of response was "initiation of cure"—that is, that in 10 to 21 days the course of the disease was reversed, the skin lesions healed, oedema disappeared, and the serum albumin content rose significantly. Since the number of cases studied was small the results were checked by means of nitrogen balance studies.

It was found that either of the amino-acid mixtures (given together with vitamins, glucose, and minerals) initiated a cure. Even without added vitamins both mixtures produced a partial response, and in a few cases a full response was obtained with the 18-amino-acid preparation alone. A level of nitrogen retention comparable to that produced by skimmed milk was obtained with the 18-amino-acid formula, and a somewhat lower level with the 11-amino-acid formula. The authors conclude that amino-acids are the chief limiting nutrients in the diet of patients in whom kwashiorkor develops, but much further work on the quantitative and qualitative requirements of amino-acids remains to be done.

David Friedberg

529. **Abnormal Brain Wave Patterns in Kwashiorkor**
R. ENGEL. *Electroencephalography and Clinical Neurophysiology* [*Electroenceph. clin. Neurophysiol.*] **8**, 489–500, Aug., 1956. 11 figs., 12 refs.

The author, working at the University of Ceylon, Colombo, has studied the electroencephalographic (EEG) findings in 25 children with kwashiorkor. Except in 2 mild cases in which the characteristic symptoms of dermatosis with depigmentation and oedema were not accompanied by the usual apathy, the EEG was invariably abnormal.

The abnormality in the EEG took the form of diffuse slowing of the dominant frequency, and in 7 fatal cases there was a steady deterioration in the records, which usually showed generalized delta activity even before the patients became comatose. The other children recovered with a high-protein diet and vitamin supplements, the EEG improving concurrently and eventually returning within the normal limits for the patient's age, save in 2 cases in which the author suggests that there may have been permanent damage to the brain from malnutrition.

John N. Walton

530. **Pyrimethamine (Daraprim) in the Control of Epidemic Malaria**
J. M. D. ROBERTS. *Journal of Tropical Medicine and Hygiene* [*J. trop. Med. Hyg.*] **59**, 201–208, Sept., 1956. 1 fig., 8 refs.

The area chosen for this experiment in the control of epidemic malaria by mass treatment of the population was situated in the Kenya Highlands at a height of 5,500 to 7,000 ft. (1,676 to 2,133 m.) and known as the Nandi Reserve. Malaria had probably been introduced to the area by soldiers returning from the war of 1914–18 and frequent epidemics have been noted since. *Anopheles gambiae* and to a lesser extent *A. funestus* are the vectors in the short transmission period which lasts from May to July each year. A survey in 1952 showed that the parasite rate was 77% among children under the age of 10.

The object of the experiment, begun in 1953, was to test the value of a single therapeutic dose of "daraprim" (pyrimethamine) given to everyone in the area; treatment was begun in May, one month after the onset of the rains, and the population of a contiguous control area was left untreated as a control. After intensive propaganda and the setting-up of treatment centres, daraprim was given in the following dosages: infants under 1 year, half a tablet (12·5 mg.); children aged 1 to 12, 25 mg.; and all persons over 12, two tablets (50 mg.). The same procedure was followed the next year (1954).

During 1953 the parasite rate fell from 23 to 2·3%, and during 1954 from 12 to 8% in the treated area, whereas in the control area it rose from 18 to 50% in 1953 and from 20 to 50% in 1954. The total cost of the treatment of 156,000 persons in the 2 years was £1,220, that is, less than twopence per head per annum, and the local inhabitants were enthusiastic over the result.

It was considered, however, that a continuation of mass treatment would be inadvisable as it might easily uncover resistant strains which would run riot through a malaria-susceptible community. It is considered that residual insecticides will be more effective in the long run though more costly.

Clement C. Chesterman

531. **Yellow Fever in Central America: the Imminent Threat to Mexico and the United States**
N. W. ELTON. *American Journal of Public Health* [*Amer. J. publ. Hlth*] **46**, 1259–1265, Oct., 1956. 1 fig., 37 refs.

Allergy

532. **Controlled Trial of Effects of Cortisone Acetate in Chronic Asthma**
MEDICAL RESEARCH COUNCIL SUBCOMMITTEE ON CLINICAL TRIALS IN ASTHMA. *Lancet* [*Lancet*] **2**, 798–803, Oct. 20, 1956. 5 refs.

The report of the subcommittee appointed by the Medical Research Council to investigate the value of cortisone acetate in chronic asthma is presented. The trial was carried out at five centres in London and one in Manchester. Patients with severe broncho-pulmonary infection, cardiac failure, or tuberculosis were excluded from the trial, and only those patients were included who were between 14 and 60 years of age, had a history of asthma of not less than 3 months' duration, and had not had complete remission for more than 2 weeks during the preceding 3 months. In all, 96 patients were studied, 49 receiving cortisone and 47 (the control group) a placebo. The groups were constituted by random allocation, and although there was a slightly higher proportion of younger women in the control group, they were otherwise comparable. The dosage of cortisone was 300 mg. on the first day, 200 mg. on the second, and 100 mg. on each of the next 4 days, the subsequent dosage being adjusted to the patient's requirements. Nearly all the patients in both groups also received some antispasmodic therapy when this was considered to be necessary.

The trial lasted 24 weeks, during which time 10 controls and 9 test patients had to be withdrawn for reasons given. Whereas at the beginning of the trial the cortisone-treated patients seemed to benefit, by the end of the trial there was no significant difference between the groups, either in regard to greater capacity for work or to the amount of antispasmodics required. The vital capacity fluctuated in both groups of patients. Two patients developed status asthmaticus in spite of receiving 100 and 75 mg. of cortisone respectively daily.

Kate Maunsell

533. **Controlled Trial of Effects of Cortisone Acetate in Status Asthmaticus**
MEDICAL RESEARCH COUNCIL SUBCOMMITTEE ON CLINICAL TRIALS IN ASTHMA. *Lancet* [*Lancet*] **2**, 803–806, Oct. 20, 1956. 5 refs.

The effectiveness of cortisone in status asthmaticus was compared with that of antispasmodic drugs in a clinical trial carried out at 13 different centres in Great Britain by a subcommittee appointed by the Medical Research Council [see Abstract 532]. No patient who was under 14 years of age or who had not had at least one severe attack of asthma was included in the trial. During the first 24 hours after admission the patient's usual treatment with well-established drugs was given and only those patients were finally selected for the trial who did not respond satisfactorily. These patients were divided into two groups at random, the first receiving cortisone acetate and the second a placebo, the patient's standard treatment being continued in both groups as required. Cortisone, in divided doses, was given as follows: 350 mg. on the first day, 200 mg. on the second, after which the dose was progressively reduced by 25 mg. daily until the ninth day, the total amount of cortisone administered then being 1·25 g. The treatment of patients with placebo tablets only, without standard treatment, was rejected on ethical grounds, and for similar reasons it was agreed that treatment could be discontinued or changed as thought necessary in any particular case during the trial.

As a result of exclusion for various reasons only 32 patients finally participated in the trial, 15 receiving cortisone and 17 the placebo. Among the former, 10 were relieved of disabling bronchial obstruction by the 4th day, whereas only 4 of the 17 control patients were so relieved; but by the end of 3 months' follow-up all of these improved patients had reverted to their former asthmatic condition. *Kate Maunsell*

534. **Chronic Asthma Treated with Aerosol Hydrocortisone**
W. BROCKBANK, H. BREBNER, and C. D. R. PENGELLY. *Lancet* [*Lancet*] **2**, 807, Oct. 20, 1956. 1 ref.

In a strictly "blind" trial of the value of an aerosol of hydrocortisone hemisuccinate in the treatment of chronic asthma, carried out at Manchester Royal Infirmary, it was found that of 9 patients taking the aerosol, 6 were no better, 2 were slightly improved, and one was much improved; in the control group given an inert aerosol the corresponding figures were 4, 2, and 3. It is concluded that hydrocortisone given as an aerosol is of no value in chronic asthma. *A. D. Duff*

535. **Absorption of Inhaled Hydrocortisone**
P. M. COTES, A. MCLEAN, and J. B. SAYER. *Lancet* [*Lancet*] **2**, 807–808, Oct. 20, 1956. 2 figs., 2 refs.

In an experimental study carried out at University College Hospital Medical School, London, on 2 healthy male subjects the inhalation of hydrocortisone alcohol or of hydrocortisone acetate in the form of a powder with a mean particle size of less than 5 μ produced an increased urinary excretion of 17-hydrocorticosteroids. The inhalations were given from a powder spray held in the mouth during deep inspiration, 45 mg. of cortisone being slowly inhaled over a period of 2 to 3 hours. In the same subjects a similar increase in hydroxycorticosteroid excretion was observed after the oral administration of 40 mg. of hydrocortisone acetate, whereas no such increase occurred after the inhalation of formolized starch given as a control. It would thus appear that powdered hydrocortisone can be absorbed by inhalation and give rise to systemic effects. *Kate Maunsell*

Nutrition and Metabolism

536. **Hereditary Pellagra-like Skin Rash with Temporary Cerebellar Ataxia, Constant Renal Amino-aciduria, and Other Bizarre Biochemical Features**
D. N. BARON, C. E. DENT, H. HARRIS, E. W. HART, and J. B. JEPSON. *Lancet* [*Lancet*] **2**, 421–428, Sept. 1, 1956. 3 figs., 20 refs.

A curious new syndrome is described, affecting 4 out of 8 children of a first-cousin marriage who were investigated at the Middlesex and University College Hospitals, London. The first child, a girl, was seen in 1937 at the age of 6 and treated for " pellagra ", but it was not until the second patient, a boy aged 12, was seen in 1951 that this diagnosis was called in doubt. Clinical abnormalities in 3 of the 4 siblings included pellagra-like skin lesions with a tendency to light sensitivity, variable cerebellar ataxia, and liability to exacerbations of these signs in the presence of intercurrent infections.

Subsequent investigation of this " H " disease (from the initial of the family's surname) revealed specific biochemical abnormalities. Urinary excretion of the amino-acids cystine, lysine, and glycine was moderately increased compared with normal values, and alanine, serine, asparagine, glutamine, valine, leucine, *iso*-leucine, phenylalanine, tyrosine, tryptophan, and histidine were present in the urine in abnormally large amounts. Taurine was present in normal quantity, but proline, hydroxyproline, methionine, and arginine were not found. The defect in these cases is considered to be a highly specific disturbance of renal tubular reabsorption of amino-acids, since the plasma amino-acid pattern was normal. Since 4 out of 8 siblings showed this typical amino-acid pattern, whereas neither parent did, it is suggested that a rare recessive gene, for which the affected individuals are homozygous, is responsible. Indole compounds were also excreted in an unusual fashion, indican, tryptophan, indolylacetic acid, and an unknown indolic substance being found in the urine in constant, large amounts. The faeces also contained an excess of protoporphyrin. Although this syndrome has not previously been described, 2 cases of " pellagra " reported in England were also investigated and found to show the same amino-acid excretion pattern as the affected members of the H. family. Also, since the urine of an African patient known to be suffering from dietary pellagra showed no such abnormality, these 2 cases of " pellagra " are considered to be additional examples of the syndrome, and references suggestive of other possible cases have been found in the literature.

In 2 of the older affected siblings in this family there has been progressive mental deterioration which, it is suggested, may be related to the abnormality which occurs in phenylketonuria. If the primary defect in this new syndrome is an inherited interference with the metabolic pathway from tryptophan to nicotinic acid, then the amino-aciduria is a secondary phenomenon. Urinary loss of tryptophan and its metabolites such as indole-3-acetic acid will accentuate this metabolic block. Alternatively it is considered plausible that a primary disorder of amino-acid transport mechanisms may lead to an abnormal intestinal flora which upsets nicotinic acid utilization. Reproductions of the urinary amino-acid and indole chromatograms are presented, and the authors emphasize the importance of such investigations in establishing the diagnosis. *Kenneth Gurling*

537. **Familial Primary Rickets Resistant to Vitamin D (Phosphate Diabetes).** (Die familiäre primäre vitamin-D resistente Rachitis (Phosphatdiabetes))
R. TOBLER, A. PRADER, and W. TAILLARD. *Helvetica paediatrica acta* [*Helv. paediat. Acta*] **11**, 209–255, Sept., 1956. 12 figs., bibliography.

In this long paper 16 cases of familial primary rickets treated within the past 5 years at the University Paediatric and Balgrist Orthopaedic Clinics, Zürich, are fully reported. This disorder, which is resistant to treatment with vitamin D, resembles nutritional rickets in that: (1) deformities of the upper limbs, thorax, and spine are less common than those of the lower limbs, so that there are often stunted stature and a waddling gait; (2) the " rickety rosary ", Harrison's sulcus, lumbar lordosis, bossing of the skull, dental caries, lassitude, and bone pain occur in both conditions; (3) radiological evidence of rickets is best obtained in the bones of the lower extremities; (4) whereas the blood calcium concentration is within normal limits, the serum phosphorus level is decreased and the serum phosphatase level increased; (5) whereas urinary deposits are normal and albuminuria and glycosuria are absent, the urinary phosphorus clearance is increased and calcium excretion decreased. The two conditions differ in that in the primary vitamin-D-resistant form: (1) a hereditary factor with a dominant mutation is the rule; (2) rickets is usually not observed until the 2nd year of life, when the child begins to try to walk properly, or sometimes even later, and only rarely in the seventh to ninth month as in the case of nutritional rickets; (3) vitamin D is therapeutically active only in doses some eight times greater than those usually effective in the treatment of nutritional rickets; (4) in order to avoid regression therapy has to be maintained for months or even years on doses of one-half to one-quarter of the large initial dose; (5) although the condition may be controlled by substitution therapy it remains active throughout the period of growth and only becomes latent when growth stops; (6) effective treatment results in clinical and radiological improvement, but it has no influence on the serum phosphorus level, there being persistent hypophosphataemia.

In the differential diagnosis, vitamin-D-resistant rickets secondary to coeliac disease, renal rickets, congenital hypophosphatasia, and other disturbances of ossification and non-rachitic deformities of the lower limbs must be borne in mind. There is no evidence that familial primary rickets develops from the nutritional form; indeed,

cases of the former have been seen in children who had been given prophylactic doses of vitamin D throughout early infancy. Because of the high dosage of vitamin D required careful control by repeated biochemical examination of the serum and urine is essential for early recognition of side-effects, which are especially likely to occur during an intercurrent illness requiring bed rest. The treatment should be stopped before osteotomy is undertaken and not begun again during the period of subsequent immobilization. The authors believe that familial primary rickets resistant to vitamin-D therapy is due to an inborn error of metabolism of which little is known, but which may be an immunological resistance to vitamin D similar to that occurring during the treatment of tetany with vitamin D_2. *E. S. Wyder*

538. **A Clinical and Biochemical Study of Galactosaemia. A Possible Explanation of the Nature of the Biochemical Lesion**

G. M. KOMROWER, V. SCHWARZ, A. HOLZEL, and L. GOLBERG. *Archives of Disease in Childhood* [*Arch. Dis. Childh.*] **31**, 254–264, Aug., 1956. 15 figs., 44 refs.

From the University of Manchester the authors describe 2 cases of galactosaemia in infants in whom the diagnosis was made within the first 10 days of life. Treatment with a galactose-free diet was started immediately and when last seen at the age of 20 months and 4 years respectively both children were perfectly normal mentally and physically.

A number of investigations were carried out on the 2 patients during the short period (10 days) before galactose-free feeding was instituted. In both cases the blood galactose level rose progressively and was accompanied by a fall in the blood glucose level. Proteinuria appeared within 48 hours of milk feeding and excessive amino-aciduria within 4 or 5 days, the latter persisting for several days after milk or galactose had been withdrawn, although the blood galactose level had fallen to zero within 24 hours of withdrawal. When the children were very young (12 and 3 months respectively) milk feeding induced a metabolic acidosis probably of renal origin, with a low plasma CO_2 content, high urinary bicarbonate excretion, and high *p*H, but when the children were older no defect was found in the renal mechanism for acidification after administration of ammonium chloride.

The search for the site of the lesion was facilitated when the authors were able to show (*Biochem. J.*, 1956, **62**, 34) that the erythrocytes of patients with galactosaemia accumulate abnormal amounts of galactose-1-phosphate in the presence of galactose and that this reduced the normal glucose metabolism. They demonstrated that the site of the disturbance must be the transformation of galactose-1-phosphate to glucose-1-phosphate. This prediction was recently confirmed by Kalckar *et al.* (*Biochem. biophys. Acta*, 1956, **20**, 262) who demonstrated that uridyl transferase, one of the enzymes concerned in this transfer, is absent from the erythrocytes of galactosaemic patients.

The authors suggest that a similar defect may occur in other tissues and that the accumulation of galactose-1-phosphate with consequent inhibition of normal glucose metabolism leads to dysfunction of the kidney, liver, brain, and lens tissues. *Robert Mahler*

539. **The Preparation and Use of Anhydrous Fat Emulsions for Intravenous Feeding and Metabolic Experiments**

D. B. ZILVERSMIT, N. K. SALKY, M. L. TRUMBULL, and E. L. MCCANDLESS. *Journal of Laboratory and Clinical Medicine* [*J. Lab. clin. Med.*] **48**, 386–391, Sept., 1956. 7 refs.

Stable fat emulsions for intravenous alimentation are difficult to prepare on a small scale. At the University of Tennessee, Memphis, the authors have devised a pre-homogenized anhydrous mixture which is easily converted to an aqueous fat emulsion by the addition of water; it is prepared by dissolving 10 g. of alcohol-soluble soya-bean phosphatide in 100 ml. of pure glycerin, to which is added, with further stirring, 100 ml. of coconut oil (melting point 76° F. (24·4° C.)) to give a homogeneous mixture (anhydrous base). In aqueous fat emulsions made from this base the particles are mostly submicroscopic in size, only occasionally being 3 μ in diameter. Initial animal experiments showed that the base was usually free from pathogens. The emulsion was not stable to autoclaving, but could be made aseptically from autoclaved ingredients. (It was later shown that the base could be autoclaved if the lecithin content were reduced by 50%.) It kept well on storage; over an 11-month period the anhydrous glycerin emulsion liberated only about one-tenth of the amount of free fatty acids liberated by an aqueous emulsion made from the same ingredients by high-pressure homogenization.

The fresh emulsion, made by diluting the base with 2·5 to 4 volumes of 5% glucose, was given intravenously each day to 5 dogs in quantities furnishing 50 to 75 Cal. per day per kg. body weight for 3 weeks without ill effects, although the animals developed a marked thirst. When killed on the 21st day necropsy revealed no abnormalities, the spleen being normal in size and containing only a moderate amount of fatty globules; in 3 of these dogs there was slight haematopoiesis and haemosiderosis. In a further study on 3 different dogs which were given daily emulsion infusions furnishing 75 Cal. per kg. per day convulsions developed after about 2 weeks. At necropsy the spleen was found to be normal in size, but showed more phagocytosed fat and iron than in the first group of animals. The toxic action was shown to be due to the glycerin, for when 4 dogs were given different doses of glycerin intravenously no ill effects were observed with daily doses up to 4 ml. per kg. per hour, but with doses of 5 ml. or more per kg. per hour convulsions developed after 12 to 20 days. When large amounts of glycerin (7 to 8 ml. per kg.) were given in a single infusion to 3 dogs, all developed convulsions at the end of the infusion, during which the rectal temperature rose to 104° to 110° F. (40° to 43·4° C.). The serum calcium and magnesium levels were normal. These findings suggest that glycerin increases the excitability of the central nervous system. *M. Lubran*

Gastroenterology

540. **Osteoma of the Tongue**
R. PEIMER, D. H. DREIZIN, and Y. MASUGI. *A.M.A. Archives of Otolaryngology* [*A.M.A. Arch. Otolaryng.*] **64**, 148–150, Aug., 1956. 2 figs., 9 refs.

The authors state that only 8 cases of true osteoma of the tongue have been reported since Monsarrat's first case in 1913. The case now described from Beth Israel Hospital, New York, occurred in a 27-year-old negress, who had noticed a mass on the tongue 5 months earlier and who complained of feeling " choky and nauseous ". There was a yellowish-greyish, firm, elevated mass the size of a green pea just to the left of the midline at the level of the circumvallate papilla. The mass was easily removed with a cold snare, and the slight bleeding controlled by application of silver nitrate. Histological examination showed a layer of stratified squamous epithelium, with a zone of fibrous tissue below, covering a central mass of cancellous bone with small Haversian canals and a few marrow spaces. The diagnosis was osteoma. No other abnormality, local or general, was found.

Of the cases so far described all but one have been in women and all in patients aged between 20 and 40. In only one was there a second lesion. In all cases the tumour was situated in the posterior third of the tongue, usually near the foramen caecum. It is suggested that these growths are probably of congenital origin and may be the remnant of a branchial arch which has ossified to cancellous bone. *F. W. Watkyn-Thomas*

541. **Thickening and Contraction of the Palmar Fascia (Dupuytren's Contracture) Associated with Alcoholism and Hepatic Cirrhosis**
S. J. WOLFE, W. H. J. SUMMERSKILL, and C. S. DAVIDSON. *New England Journal of Medicine* [*New Engl. J. Med.*] **255**, 559–563, Sept. 20, 1956. 2 figs., 17 refs.

A study was undertaken to verify an earlier clinical impression that Dupuytren's contracture occurs frequently in patients with chronic alcoholism and cirrhosis of the liver treated at Boston City Hospital. Fifty-seven alcoholic patients with cirrhosis, 55 alcoholic patients without manifest liver disease, and 53 patients who were nondrinkers and had no evident liver disease were studied for prevalence of Dupuytren's contracture. In addition the files of Thorndike Memorial Laboratory [Boston] were reviewed to determine the prevalence of Dupuytren's contracture in patients with hepatic cirrhosis seen in the past 10 years.

Palmar contracture occurred in 66% of the male alcoholic patients with cirrhosis, 27% of the male alcoholic patients without liver disease, 12% of the male controls, and 42% of the male cases taken from Thorndike records. Deformity occurred at an earlier age in alcoholic patients with cirrhosis of the liver. Results in females were based on insufficient numbers of observations. The interpretation of these data is subject to limitations because of the selection of the populations studied.—[Authors' summary.]

542. **I^{131}-Labeled Fat in the Study of Intestinal Absorption**
J. M. RUFFIN, W. W. SHINGLETON, G. J. BAYLIN, J. C. HYMANS, J. K. ISLEY, A. P. SANDERS, and M. F. SOHMER. *New England Journal of Medicine* [*New Engl. J. Med.*] **255**, 594–597, Sept. 27, 1956. 7 figs., 3 refs.

This interesting paper from Duke University School of Medicine, Durham, N. Carolina, promises a new approach in the study of intestinal absorption. In previous experiments characteristic and reproducible curves of the blood level of radioactive iodine (^{131}I) were obtained in healthy subjects given albumin-containing and fat-containing test meals labelled with the isotope. The test meal used by the authors contained 25 microcuries of ^{131}I and was mixed with 20 g. of barium sulphate. [For further details of its composition the original paper should be consulted.] After ingestion of the test meal 2 ml. of venous blood was withdrawn at hourly intervals for 6 hours and its radioactivity measured; from the result the total blood level of ^{131}I was determined. All stools passed during the next 48 hours were separately collected in special containers and the ^{131}I content estimated. In the case of both blood and faeces the amount of ^{131}I recovered was expressed as a percentage of the ingested material.

Altogether 180 patients were studied, divided for convenience into three groups: (1) with functional disturbances; (2) with gastro-intestinal diseases; and (3) having previously received surgical treatment for peptic ulcer. In the 44 cases in Group 1 (functional disturbances) the amounts of radioactive material recovered from both blood and faeces were closely similar to those found in health. Of Group 2 (gastro-intestinal diseases: 57 cases), 18 cases of chronic relapsing pancreatitis, 13 of carcinoma of the pancreas, 2 of Whipple's disease, and 3 of regional enteritis showed significantly lower blood levels and greatly raised faecal levels of ^{131}I; 4 cases of sprue in clinical remission had normal values in both blood and stools, while in a fifth case of sprue, in relapse, the blood value was much reduced and the stools contained a markedly increased amount of ^{131}I; in 8 patients with ulcerative colitis and 8 with liver cirrhosis normal values were found in both blood and stools. Of the 79 patients operated upon for peptic ulcer (Group 3), 64 had had partial resection and 15 vagotomy with gastro-enterostomy; tests in this group, all of which were performed at least 6 months post-operatively, showed 53% to have abnormal ^{131}I values.

Evidence is adduced in support of the assumption that this test actually measures fat absorption, as follows. The radioactive material appearing in the blood cannot

be dialysed, thus indicating that ^{131}I is attached either to fat or to a product of its digestion; in pancreatectomized dogs the amount of the isotope recovered from the blood after a test meal containing ^{131}I-labelled fat is greatly reduced, but normal values are obtained after ingestion of ^{131}I alone; in the portal venous blood of animals ^{131}I is bound to the beta-lipoprotein fraction or to neutral fat; a reduced blood level of ^{131}I was invariably associated with a high stool content, and vice versa; and finally, the faecal fat content was the same whether a radioactive technique was used or fat-balance studies were carried out.

[The need exists for a simple and reliable test for fat absorption from the gastro-intestinal tract. Should the reliability of the authors' technique be confirmed, similar procedures could be worked out for other nutrients.]

Z. A. Leitner

STOMACH AND DUODENUM

543. **Gastric Cancer, Relationships between ABO Blood-groups, Site, and Epidemiology**

B. P. BILLINGTON. *Lancet* [*Lancet*] **2**, 859–862, Oct. 27, 1956. 15 refs.

Aird *et al.* (*Brit. med. J.*, 1954, **2**, 315; *Abstracts of World Medicine*, 1954, **16**, 464) have shown a probable association between gastric carcinoma and blood of Group A. The present author now reports an extension of this work, in which a series of 483 cases of cancer of the stomach seen at four teaching hospitals in Sydney, Australia, over 7 years were classified by site (those within 4 cm. of the pylorus being categorized as prepyloric, those within 3 cm. of the cardia as cardial, and the remainder as carcinoma of the body), and by relation to the three different types of gastric gland. No cases of diffuse gastric cancer were included. Blood-group data for the patients, when available, were compared with the distribution of ABO blood groupings in blood donors from the same geographical area in 1947.

When all patients with gastric carcinoma were compared with blood donors in regard to Groups B and AB taken together there was no significant difference in the ABO distribution. However, when the ABO distribution was analysed according to the site of the lesion in the stomach significant correlations were found. Thus patients with blood of Group O were 6·2 times more likely to develop carcinoma of the body of the stomach than those with blood of Group A, and these latter were 6·2 times more likely to develop carcinoma in the prepyloric or cardial region than those with blood of Group O. Classification by sex and by incidence of Group-B blood showed no significant differences in site. The significance and validity of these findings are considered by comparison with the results of similar investigations in England and Scotland, and with other possible associated genetic patterns, particularly pernicious anaemia. On this basis it is thought reasonable to deduce an association of blood of Group O with carcinoma of the gastric body and blood of Group A with carcinoma of the prepyloric and cardial regions. This association is considered to be additional to the genetic influences predisposing to the inheritance of gastric carcinoma itself, and the author discusses the possibility that it may depend on the secretor status of ABO blood-group mucoids by the different types of gastric gland. If such an association is accepted, differences in blood-group gene frequencies and the incidence of gastric carcinoma at different sites may be expected to be related in different populations, and available figures for London and Sydney appear to support this expectation.

[In this type of investigation the study of siblings is desirable and valuable.]

W. A. Bourne

544. **Studies on the Physiology of Hunger. I. The Effect of Intravenous Administration of Glucose on Gastric Hunger Contractions in Man**

A. J. STUNKARD and H. G. WOLFF. *Journal of Clinical Investigation* [J. clin. Invest.] **35**, 954–963, Sept., 1956. 2 figs., 31 refs.

In experiments carried out at the New York Hospital–Cornell Medical Center on 3 healthy subjects and 20 patients with various diseases (including 5 with diabetes mellitus) intravenous injections of 50 ml. of 50% glucose solution were given at times when an intragastric balloon recording device showed vigorous contractions of the stomach wall. Venous and capillary blood samples were taken at intervals during the next hour. In 19 out of 40 experiments the contractions ceased within 5 minutes of the injection, and in this group the mean difference in glucose level between capillary and venous blood 10 and 20 minutes after the injection was significantly greater (at the 5% level) than in the 16 experiments in which the gastric contractions persisted for at least 20 minutes after the injection. The results of the remaining experiments could not be classified. The conclusion is drawn that an increased rate of peripheral removal of glucose, as evidenced by the difference between capillary and venous blood, is associated with a decrease in gastric hunger contractions.

[In 5 subjects the gastric contractions were inhibited in some experiments but persisted in others. If these 5 cases, where each subject is his own control, are considered separately, the results fail to support the authors' conclusions.]

Denys Jennings

545. **Tea-drinking and Gastritis**

F. C. EDWARDS and J. H. EDWARDS. *Lancet* [*Lancet*] **2**, 543–545, Sept. 15, 1956. 1 fig., 15 refs.

An investigation was undertaken at the Central Middlesex Hospital, London, to determine whether intake of very hot drinks was associated with abnormalities of the gastric mucosa, the subjects of the investigation being 155 patients on whom gastric biopsy had recently been performed because of dyspepsia. The histological appearances of the biopsy specimens were classified as normal (78 cases), miscellaneous (32), superficial gastritis (9), and atrophic gastritis (36). Each patient was given a cup of boiling tea, flavoured to taste, and asked to sip it frequently. When it had cooled to the temperature at which it was usually drunk this temperature was recorded. In nearly every case the observer of the temperature was unaware of the histological report.

There was a clear association between a rising temperature at which the tea was drunk and progressive mucosal abnormality which was not explicable on grounds of age and sex. Of patients under 50 years, only 2 out of 13 who drank tea when it was below 122·5° F. (50·27° C.) had an abnormal mucosa, whereas 14 out of 18 who drank tea when it was 137·5° F. (58·6° C.) had an abnormal gastric mucosa. *T. D. Kellock*

546. **Alkali Requirement for Continuous Neutralisation of Gastric Contents in Gastric and Duodenal Ulcer**

A. V. PRICE and P. H. SANDERSON. *Clinical Science* [*Clin. Sci.*] **15**, 285–295, May, 1956. 9 figs., 24 refs.

In a study of the role of gastric acidity in the production of peptic ulceration, carried out at St. Mary's Hospital, London, analyses of gastric acidity were carried out over periods of 24 hours in 10 cases of gastric and 19 cases of duodenal ulcer. The difference in the acidity pattern in these two conditions was confirmed. The oral administration of 4 g. of an alkaline powder composed of sodium bicarbonate, calcium carbonate, light magnesium carbonate (3 parts each), and bismuth carbonate (1 part) partially controlled the acidity in patients with gastric ulcer, but was much less effective in those with duodenal ulcer.

The alkali requirement for the continuous neutralization of the gastric contents was then studied in 15 cases of gastric ulcer and 15 of duodenal ulcer in which an intragastric drip consisting of 3 litres of milk per 24 hours was administered at a rate of 60 ml. in each half-hour period, the amount of added sodium bicarbonate required to keep the gastric *p*H at or above 4 being determined. This amount varied from 20 to 60 g. in 13 of the 15 patients with gastric ulceration, the remaining 2 patients requiring 140 and 160 g. respectively. In the patients with duodenal ulcer the range was 60 to 140 g., 11 of the 15 patients requiring between 80 and 100 g. The intragastric milk-drip with added sodium bicarbonate was well tolerated up to periods of 3 weeks provided that a soft, small-bore, rubber nasal tube was used. Symptomatic relief was marked, and there was no incidence of clinical alkalosis. *R. Schneider*

547. **Effects of Tricyclamol on Gastric Secretion and Gastrointestinal Motility in Peptic Ulcer. Experimental Studies and Clinical Observations**

A. M. KASICH, A. P. BOLEMAN, and J. C. RAFSKY. *American Journal of Digestive Diseases* [*Amer. J. dig. Dis.*] **1** (New Series), 361–379, Sept., 1956. 17 refs.

A synthetic anticholinergic drug, tricyclamol (1-*cyclo*hexyl-1-phenyl-3-pyrrolidino-1-propanol methchloride), was tried at the Lenox Hill Hospital, New York, in the treatment of patients with peptic ulcer. Preliminary investigations showed that in 9 patients with duodenal ulcer and one with gastric ulcer the acidity of the fasting gastric juice was reduced after administration through a Levin tube of 100 mg. of tricyclamol suspension. The same dose reduced the acidity in 6 patients given 200 ml. of 5% alcohol, but did not lessen the acidity of gastric secretion in 10 patients given insulin. In 10 patients with peptic ulcer motility of the stomach and small intestine was studied in radiographs taken 15, 30, and 60 minutes after ingestion of barium, which was given one hour after oral administration of 100 mg. of tricyclamol. The drug caused a decrease in gastric peristalsis and slowed transit through the small intestine.

Tricyclamol was given in a dosage of 50 mg. four times a day to 105 patients with chronic peptic ulcer. In 76 complete relief was obtained; in 24 the results were fair, there being intermittent dyspepsia; and in 5 the results were poor. Side-effects were few—the drug had to be withdrawn in one case because of severe xerostomia, in 4 cases constipation was troublesome, and in one blurring of vision was severe. Urination was not affected. In 10 patients experimentally-induced peptic-ulcer pain could be abolished by intravenous administration of 20 mg. of tricyclamol. The authors conclude that tricyclamol is a valuable therapeutic adjuvant in the management of patients with peptic ulcer.

T. J. Thomson

548. **Late Results of Vagotomy Combined with Gastro-jejunostomy or Pyloroplasty in the Treatment of Duodenal Ulceration**

J. A. L. DAVIES. *British Medical Journal* [*Brit. med. J.*] **2**, 1086–1091, Nov. 10, 1956. 26 refs.

The author compares the results obtained in 198 cases of chronic duodenal ulcer treated by vagotomy and gastro-jejunostomy with those in 132 cases treated by vagotomy and pyloroplasty. The 330 patients were operated on at several different centres in Great Britain and the cases were reviewed between 4 and 7 years after the operation, about half (47%) by interview and half by means of a questionary. Over-all satisfactory results were obtained in 90·6% of the cases, 21·8% of the patients had gained weight, 65% had a steady normal weight, but 22·5% complained of diarrhoea, which was troublesome in 3%. Some 14% suffered from mild hypoglycaemic attacks, with faintness and sweating one to 2 hours after eating, which was relieved by taking food. Delayed gastric emptying was noted in 8 patients, all of whom had been treated by pyloroplasty. Recurrent peptic ulceration occurred in 6 patients (4·5%) after vagotomy and pyloroplasty (2 having gastric ulcer), compared with 11 (5·6%) after vagotomy and gastro-jejunostomy (9 having stomal and 2 gastric ulcer).

The other differences between the two types of operation were (1) a higher number of unsatisfactory results after vagotomy and pyloroplasty (9·1% compared with 4% after vagotomy and gastro-jejunostomy), and (2) a higher incidence of hypoglycaemic attacks after pyloroplasty (20% compared with 11% after gastro-jejunostomy). Recurrent duodenal or stomal ulceration occurred in no case in which the vagotomy was shown by an insulin test meal to be complete. The author concludes that vagotomy compares favourably with partial gastrectomy, particularly in its lower mortality and the better postoperative nutritional state of the patient. The results in women were as good as in men. In his opinion gastro-jejunostomy is a better accessory operation to vagotomy than is pyloroplasty.

Norman C. Tanner

Cardiovascular System

549. **Cardiac Amyloidosis**
R. BENSON and J. F. SMITH. *British Heart Journal* [*Brit. Heart J.*] **18**, 529–543, Oct., 1956. 13 figs., 29 refs.

In this paper from the London Hospital the authors describe 5 cases of primary amyloidosis in which the presenting symptoms were those of heart disease, and draw attention to the condition as a cause of heart failure.

All 5 patients were females and were aged between 46 and 63 years of age. In 3 cases the cause of the heart failure was not clear during life, in one the electrocardiographic findings were suggestive of a myocardial infarction, while in the fifth constrictive pericarditis had been suspected and the patient subjected to a fruitless thoracotomy. Generalized cardiac enlargement, absence of murmurs, and normal or low blood pressure were the rule. The electrocardiograms were of low voltage in 3 cases, with evidence of right bundle-branch block in 2.

At post-mortem examination, carried out in all 5 cases, amyloid infiltration of the heart was macroscopically evident in 4 cases and microscopically extensive in all 5. Amyloid tissue was found scattered in varying small amounts in other parts of the body, notably the pulmonary arteries, spleen, and kidneys—a finding in agreement with that of previous workers. Thus primary amyloidosis affects chiefly the heart and skeletal and smooth muscle, and only slightly the liver, spleen, kidneys, and adrenal glands, and heart failure is the usual cause of death. The authors stress that recognition of the disease during life is difficult, but that the diagnosis should always be considered in cases of unexplained heart failure, especially if accompanied by hypotension and an electrocardiogram showing low voltage and conduction defects. *Joan Yell*

DIAGNOSTIC METHODS

550. **The Electrocardiogram in Infarction of the Lateral Wall of the Left Ventricle. A Clinicopathologic Study**
W. J. DUNN, J. E. EDWARDS, and R. D. PRUITT. *Circulation* [*Circulation (N.Y.)*] **14**, 540–555, Oct., 1956 (Part I). 8 figs., 8 refs.

For this study the authors have analysed 30 cases of myocardial infarction of the lateral wall of the left ventricle—defined as the area including the posterior half of the anterior papillary muscle and extending to the anterior border of the posterior papillary muscle—seen at the Mayo Clinic between 1947 and 1955, and for which adequate electrocardiographic and post-mortem evidence was available. The major conclusion is that " infarcts of the lateral wall of the left ventricle, particularly in their acute phases, are not electrocardiographically ' silent '; their voice, however, is one of weak and mingled tones ". Although segmental elevation and subsequent inversion of T waves occurred commonly in leads presumably so oriented as to face the epicardial aspect of the infarcted myocardium, there was no consistently recurring pattern. Additional leads from the upper left part of the praecordium and left axilla did not prove helpful, as they mostly confirmed changes in the more conventional leads and aV_1, but it is suggested that it may be of value to record the potentials from the left arm in any patient suspected of having myocardial infarction. *W. A. R. Thomson*

551. **Electrocardiographic Studies of Cases with Intracardiac Malformations of the Atrioventricular Canal**
E. TOSCANO-BARBOSA, R. O. BRANDENBURG, and H. B. BURCHELL. *Proceedings of the Staff Meetings of the Mayo Clinic* [*Proc. Mayo Clin.*] **31**, 513–523, Sept. 19, 1956. 6 figs., 14 refs.

Certain characteristic features of the electrocardiogram (ECG) in 16 cases of persistent common atrio-ventricular canal (C.A.V.C.) are presented in this paper from the Mayo Clinic. In right praecordial leads an rSR pattern simulating partial right bundle-branch block is seen, as in cases of pure atrial septal defect, but limb leads show left axis deviation and dominant positivity in aVR. In the vectorcardiogram the frontal QRS loop is inscribed in a counter-clockwise direction and lies mainly above the iso-electric point. This position is diametrically opposed to that seen in most other cases of congenital heart disease with right bundle-branch block. This loop illustrates the important features in scalar leads, namely, the negative deflections in aVF, the positive deflections in aVL, and the Q and prolonged R in aVR.

In 9 cases of C.A.V.C. with high pulmonary flow but little or no right ventricular hypertension the mean electrical axis lay between −90 and −115 degrees, and either overloading occurred in neither ventricle or overloading was balanced; aVL showed a qRS pattern, aVF showed rS, and aVR a prolonged R with q or Q, while V1 showed right bundle-branch block. In 5 cases of C.A.V.C. with right ventricular hypertension the mean electrical axis lay between −175 and −135 degrees. The ECG differed from that of other cases of right ventricular hypertension by the direction of inscription and its position above the iso-electric line. The recordings from Lead V1 suggested right ventricular hypertrophy, with a very tall R or R′. In 2 cases of C.A.V.C. with mitral incompetence or large interventricular left-to-right shunt the mean electrical axis was about −60 degrees. In these cases aVL showed qRS or qRs, aVF showed rS, and aVR showed QR. R was high in left chest leads. In many cases P–R was significantly prolonged.

The authors suggest that the characteristic ECG is the result of a fundamental alteration in ventricular excita-

tion pathways due to the defect at the top of the ventricular septum. They stress that these patterns, though suggestive, are not pathognomonic, since similar ECGs have been seen in cases of hypertensive heart disease with left ventricular hypertrophy and right bundle-branch block, in cases of cor pulmonale, and in coronary disease.

D. Emslie-Smith

CONGENITAL HEART DISEASE

552. **Developmental and Pathologic Considerations in Persistent Common Atrioventricular Canal**

C. S. WAKAI and J. E. EDWARDS. *Proceedings of the Staff Meetings of the Mayo Clinic* [*Proc. Mayo Clin.*] **31**, 487–500, Sept. 5, 1956. 3 figs., 11 refs.

In this contribution to a symposium on persistent common atrioventricular canal held at the Mayo Clinic the authors outline the embryological development of the dorsal and ventral atrio-ventricular cushions in relation to the division into right and left sides of the embryonic common atrium, common atrio-ventricular canal, and common ventricle. These endocardial cushions form part of the interatrial septum primum, of the ventricular septum, of the anterior (aortic) leaflet of the mitral valve, and of the medial (septal) leaflet of the tricuspid valve.

Hence if the two atrio-ventricular cushions fail to fuse with each other and with the atrial and the ventricular septa, persistence of the common atrioventricular canal results in its complete form. The anterior mitral cusp and the septal tricuspid cusp are each cleft, the clefts being continuous along the horizontal line of failure of fusion. There is thus a communication between the mitral and tricuspid orifices running between the anterior and posterior leaflets of a common atrioventricular valve. The interatrial defect has a crescentic upper border and lies anterior to the right atrial coronary-sinus ostium and below the ostium secundum. When the foramen ovale is abnormal the lower limbus of the septum secundum is absent or rudimentary. The nature of the interventricular defect depends on the attachment of the under surface of the common atrio-ventricular valves to the ventricular septum. Interventricular communication may exist through the posterior muscular septum or beneath the anterior or posterior cusps of the common valve, with absence of the membranous part of the septum.

When only the left-sided cushions fail to fuse, then a partial persistent common atrio-ventricular canal results, the tricuspid valve being normal and the anterior mitral cusp being cleft. The lower edge of the interatrial defect is the intact tricuspid septal cusp. Usually the inferior aspects of the mitral anterior septal cusps and of the tricuspid septal cusps are joined to the upper part of the ventricular septum by fused chordae which prevent anatomical interventricular communication. Occasionally transitional cases occur, with clefts in both the anterior mitral cusp and the septal tricuspid cusp, but no union between the tricuspid and mitral orifices.

The authors analyse 22 cases of the anomaly, which in 14 cases was complete, in 5 partial, and in 3 transitional. Two patients with partial anomaly survived to the ages of 27 and 37 years respectively. The longest survival of a patient with the complete form of anomaly in this series was 16 months, but one case of survival to 22 years of age has been reported. A patent foramen ovale was an associated defect in 3 of the cases of partial anomaly and in all cases of the complete anomaly.

D. Emslie-Smith

553. **Hemodynamic Data and Findings of Diagnostic Value in Nine Proved Cases of Persistent Common Atrioventricular Canal**

C. S. WAKAI, H. J. C. SWAN, and E. H. WOOD. *Proceedings of the Staff Meetings of the Mayo Clinic* [*Proc. Mayo Clin.*] **31**, 500–508, Sept. 5, 1956. 4 figs., 9 refs.

This report records the haemodynamic data obtained by cardiac catheterization and dye dilution techniques in 11 cases (5 in adults and 6 in children) of proved persistent common atrio-ventricular canal studied at the Mayo Clinic. In 4 of the adults and in all the children there was a left-to-right shunt, the adults having normal intracardiac pressure and the children slight or moderate pulmonary hypertension, while the fifth adult had pulmonary hypertension with a right-to-left shunt. In all cases the systemic blood flow was normal. In 7 out of 9 cases pulmonary flow was greater than systemic, mainly because of the atrial septal defect. Evidence of valvular incompetence was not revealed in atrial or wedge-pressure tracings and in most cases was not found on physical examination either.

Three points were found useful in distinguishing persistent common atrio-ventricular canal from simple atrial septal defect. (1) When the tip of the catheter is lying in the left ventricle the shaft lies low in the cardiac shadow in cases of common atrio-ventricular canal, but occupies a mid-way position in simple atrial septal defect (6 cases out of 9). (2) In cases of common atrioventricular canal the blood in the right ventricle is more highly oxygenated than in the right atrium, thus confirming the presence of a ventricular as well as an atrial septal defect (7 cases out of 10). (3) If dye is injected into the right and left pulmonary arteries the dilution curve in simple atrial septal defect usually shows that there is a greater left-to-right shunt of right-lung than of left-lung blood, because the orifices of the right pulmonary veins are nearer the defect; this finding is less common in cases of atrio-ventricular canal, in which the two dilution curves resemble each other. It is suggested that on the basis of these findings a common atrioventricular canal may be strongly suspected though not diagnosed with certainty. *D. Emslie-Smith*

554. **Clinical Features of Persistent Common Atrioventricular Canal**

R. O. BRANDENBURG and J. W. DUSHANE. *Proceedings of the Staff Meetings of the Mayo Clinic* [*Proc. Mayo Clin.*] **31**, 509–513, Sept. 19, 1956. 7 refs.

The cardiac septal defect taking the form of a persistent common atrio-ventricular canal (C.A.V.C.) is generally stated to be rare, but experience at the Mayo Clinic and a review of previous reports on the surgical treatment of

atrial septal defect showed that 10 to 15% of such cases were of the C.A.V.C. variety. Since atrial septal defect is the commonest congenital cardiac lesion, C.A.V.C. is probably commoner than has been supposed. While the lesion is often serious and may result in early death, patients with it, especially in its partial form, may reach adult life with only mild to moderate symptoms and little or no valvular insufficiency. Accurate diagnosis of the lesion is important, for mitral incompetence due to a cleft valve cusp can sometimes be abolished by direct suture, and while simple atrial septal defect can be operated on by means of the atrial-well technique, C.A.V.C. is best tackled with the help of an extra-corporeal circulation.

The clinical features of the condition are very varied, but are basically those of atrial septal defect with or without signs of ventricular septal defect and of tricuspid or mitral incompetence. The most important physical sign which differentiates C.A.V.C. from uncomplicated atrial septal defect is a harsh murmur at the lower left sternal border and/or apex, due to incompetence of one or both of the atrio-ventricular valves. But haemo-dynamic features may modify the clinical findings; for example, sometimes a systolic regurgitant jet is forced from the left ventricle into the right atrium, or if tri-cuspid incompetence exists as well, the right atrium may receive blood from all three other chambers. The effects of the left ventricular load may be masked by right ventricular hypertrophy, while pulmonary hypertension may reverse the left-to-right shunt.

The authors suggest classification of C.A.V.C. into three clinical types, as follows: (1) atrial septal defect (ostium primum type) without valvular insufficiency, in which pulmonary hypertension is relatively infrequent; (2) septal defect (ostium primum type) with insufficiency of the mitral valve or both mitral and tricuspid valves; here pulmonary hypertension is more often found; (3) atrial septal plus ventricular septal defect plus in-sufficiency of the atrio-ventricular valves, in which pul-monary hypertension is common.

D. Emslie-Smith

555. **The Surgical Treatment of Persistent Common Atrioventricular Canal: Report of 12 Cases**

J. C. Cooley and J. W. Kirklin. *Proceedings of the Staff Meetings of the Mayo Clinic* [*Proc. Mayo Clin.*] **31**, 523–527, Sept. 19, 1956. 1 fig., 8 refs.

When a persistent common atrio-ventricular canal (C.A.V.C.) has been diagnosed the authors suggest that surgical treatment should be advised unless pulmonary hypertension has produced a right-to-left shunt. Open cardiotomy, with an extracorporeal circulation through a pump-oxygenator, is the best technique. The right atrium is first explored by a finger through the auricular appendage and any atrio-ventricular regurgitation is noted. The right atrium is then opened by a long vertical incision. The detailed procedure of repair depends on the anatomical details of the defect. A cleft, incompetent mitral valve is sutured with silk. The defect is then obliterated with shaped " ivalon " sponge (4 mm. thick) fastened by interrupted silk sutures, first to the bare area of ventricular septum, then forward and backward as far as the junction of the atrial septum with the rings of the atrio-ventricular valves.

This operation has been performed at the Mayo Clinic on 12 patients ranging in age from 10 months to 27 years, 5 of them being aged over 20. Of these 12 patients, all of whom had symptoms and 7 had mitral incompetence, 9 survived the operation. In one case cardiac catheterization revealed complete closure 6 months later, and in the other 7 an excellent clinical result was achieved. Of the 3 children who died, one had severe pulmonary hypertension and another had severe mitral incompetence which was unrelieved by operation.

D. Emslie-Smith

556. **Anatomic and Pathologic Studies in Ventricular Septal Defects**

L. M. Becu, R. S. Fontana, J. W. DuShane, J. W. Kirklin, H. B. Burchell, and J. E. Edwards. *Circulation* [*Circulation* (*N.Y.*)] **14**, 349–364, Sept., 1956. 5 figs., 6 refs.

In this paper from the Mayo Clinic the authors analyse the necropsy findings in 50 cases of ventricular septal defect. Anatomically, in 36 cases the defects were related to the membranous part of the septum; the left ventricular face lay immediately below the right and posterior aortic cusps, and the right ventricular face was partly covered by the septal cusp of the tricuspid valve, lying low and posteriorly in the outflow part of the right ventricle. Twenty of these defects were small and 16 large, having a cross-sectional area as big as, or bigger than, that of the aorta. In the bigger defects the aortic valve ring lay partly over the right ventricular cavity, giving the impression of dextroposition. Four other defects involved the higher part of the outflow tract of the right ventricle and were large; 11 were lower, in the muscular part of the septum, and were small. (These figures total 51, as one heart had 2 defects.) The septal defect was the sole abnormality in 34 of the 50 cases; in 19 of these it was considered to be the main cause of death; the usual mode of death was left ventricular failure, and this occurred in all 12 deaths under 1 year of age; two older children died of bacterial endo-carditis, and 2 adults of congestive heart failure. In 16 of the 50 cases there were other cardiovascular abnormalities.

Altogether 20 patients died before the age of 1 year. The defects here tended to be large, contrasting with the smaller defects in patients dying in adult life of bacterial endocarditis, in whom there would be a pres-sure difference between the ventricles and a vigorous jet of blood. It is suggested that survival to adult life with a large defect may be dependent upon the develop-ment of a high pulmonary vascular resistance restricting the volume of the pulmonary blood flow and of the shunt.

J. A. Cosh

557. **Atrial Septal Defect in the Aged**

N. Coulshed and T. R. Littler. *British Medical Journal* [*Brit. med. J.*] **1**, 76–80, Jan. 12, 1957. 9 figs., 7 refs.

558. **Aortic Subvalvar Stenosis. A Report of 5 Cases Diagnosed during Life**

R. BROCK and P. R. FLEMING. *Guy's Hospital Reports* [*Guy's Hosp. Rep.*] **105**, 391–408, 1956. 6 figs., 24 refs.

Five cases of aortic subvalvar stenosis are described, all diagnosed during life and treated by operation. The ages of the patients were 7, 9, 17, 24 and 58; 2 were male and 3 were female. In all cases the preoperative diagnosis was the generic one of aortic stenosis. The differentiation from valvar stenosis was made in 4 by pressure records made with a catheter slowly withdrawn from the aorta into the left ventricle. In one case this failed to show the stenosis was subvalvar; this was identified at open operation when the valve was exposed to view. In another case valvar and subvalvar stenosis co-existed; the subvalvar being the more important. It is pointed out that the various clinical and indirect instrumental methods suggested as a means of differentiation are unreliable. The only methods likely to succeed preoperatively in demonstrating a subvalvar stenosis are angiocardiography and a withdrawal pressure recording using a catheter; so far we have not succeeded in obtaining a withdrawal pressure record in this way before operation.

Two of the 5 patients died from operation; in both of these the lesion was virtually inoperable. In 2 cases resection and in one case dilatation gave a good result with substantial relief of stenosis. The dangers of blind punch resection from below are presented. The possibility of open dilatation from above is discussed and also the difficulties of adequate surgical exposure of the aortic subvalvar region to allow leisured, precise resection of the stenosis under direct vision. It is suggested that this may be possible in some cases by carrying an aortic incision down into the ventricle through a commissure; in others it may be possible to approach the region by traversing the infundibulum of the right ventricle and the ventricular septum. In yet others safe direct exposure may be impossible. In general, however, the condition should not be rejected as unsuitable for operative relief. —[Authors' summary.]

559. **Tricuspid Atresia**

J. W. BROWN, D. HEATH, T. L. MORRIS, and W. WHITAKER. *British Heart Journal* [*Brit. Heart J.*] **18**, 499–518, Oct., 1956. 14 figs., 43 refs.

Eight patients with congenital tricuspid atresia and one with congenital tricuspid stenosis are described, with an account of the autopsy findings in 4 of them. Characteristic symptoms were breathlessness on exertion, cyanosis, and recurrent chest infections but these are not specific to tricuspid atresia. On physical examination, central cyanosis and finger clubbing occurred in all, and a praecordial systolic murmur in all but one. A palpable thrust at the apex indicated left ventricular hypertrophy in 2 patients but in the others the clinical signs were suggestive of Fallot's tetralogy. The jugular venous pulse, although abnormal in 6, was not characteristic enough to be diagnostic.

The electrocardiogram was recorded in 8 patients and showed left axis deviation in all. This was considered a most important diagnostic feature since it excluded the diagnosis of Fallot's tetralogy and suggested the probability of tricuspid atresia. Abnormally tall P waves occurred in only 2 patients. Radiological examination was suggestive of tricuspid atresia in only 2 of the patients who showed square-shaped hearts. Generally, in tricuspid atresia the cardiac silhouette will be compatible with a diagnosis of Fallot's tetralogy. Angiocardiography provided confirmatory diagnostic evidence in 7 of the 8 patients in whom it was done. Early filling of the left ventricle and a "right ventricular window", sometimes showing a diminutive right ventricle later, are pathognomonic signs in the antero-posterior views. The origin of the great vessels was well seen in the lateral views and there was evidence of transposition in only one of the patients. Cardiac catheterization was performed in 2 patients. It provided anatomical confirmation of an atrial septal defect and suggested tricuspid atresia from inability to introduce the catheter into the right ventricle. Generally it is an unnecessary diagnostic procedure.

Autopsy examination of the heart in 3 cases showed classical abnormalities of tricuspid atresia and in a fourth, who was a mongol, an associated patent foramen primum. Histological examination of the small pulmonary vessels was normal in the youngest patient aged 3 months, but in another aged 7 years showed great reduction of the pulmonary vascular bed due to extensive thrombosis in pulmonary arteries and veins. These pathological changes offered an explanation of the failure of anastomotic operations in 4 of our patients. It is suggested that anastomotic operations are more likely to be successful when carried out in infancy before the secondary pulmonary vascular changes develop.—[Authors' summary.]

560. **Five-year Postoperative Results of First 500 Patients with Blalock–Taussig Anastomosis for Pulmonary Stenosis or Atresia**

B. D. WHITE, D. G. MCNAMARA, S. R. BAUERSFELD, and H. B. TAUSSIG. *Circulation* [*Circulation (N.Y.)*] **14**, 512–519, Oct., 1956 (Part I). 4 figs., 4 refs.

This report from the Johns Hopkins Hospital, Baltimore, concerns the fate of the first 500 patients subjected to the operation of subclavian–pulmonary anastomosis by Blalock or one of his associates from November, 1944, to September, 1947. Of this number, 81 died at, or within 6 months of, operation, and on 30 an exploratory thoracotomy alone was carried out. For various reasons only 244 of those who were originally improved by the operation were available in 1952 with sufficient data for inclusion in this survey 5 to 8 years after operation. Results were classified as "good" (93%) or "fair" (7%), a good result implying a virtually normal exercise tolerance and nearly normal erythrocyte count, haemoglobin level, and haematocrit value.

Five years or more later 163 patients (67%) had maintained their improvement, 23 had undergone, and survived, a second operation, and 33 had died. The fate of those whose result was originally classified as fair was worse than that of those with a good result

(44% fatality rate compared with 11%). The prognosis has also been much better for patients with Fallot's tetralogy than for those with other abnormalities (69% of those with Fallot's tetralogy were doing well after 5 years compared with 50% of those with other abnormalities, and the respective late mortalities were 11% and 31%). Further analysis of the cases with a good result showed a fall in haemoglobin level and erythrocyte count to near normal in the majority of cases. Arterial oxygen saturation was above 75% in all the cases, and in many was between 90 and 100%. In 15 cases (6%) subacute bacterial endocarditis developed, although positive blood cultures were obtained only in 8 of these. Only one patient died from the infection. Of the 33 late deaths, only 2 were due to cardiac failure, and neither patient had Fallot's tetralogy; 7 patients died as a result of a second operation, and the remainder from a wide variety of causes. *W. P. Cleland*

561 (*a*). **Endocardial Fibro-elastosis. I. Endocardial Fibro-elastosis Associated with Congenital Malformation of the Heart**

D. H. ANDERSEN and J. KELLY. *Pediatrics* [*Pediatrics*] **18**, 513–538, Oct., 1956. 1 fig., 31 refs.

561 (*b*). **Congenital Endocardial Fibro-elastosis. II. A Clinical and Pathologic Investigation of Those Cases without Associated Cardiac Malformations Including Report of Two Familial Instances**

J. KELLY and D. H. ANDERSEN. *Pediatrics* [*Pediatrics*] **18**, 539–555, Oct., 1956. 35 refs.

In the first of the two studies here reported from the College of Physicians and Surgeons (Columbia University), New York, 129 cases of congenital heart disease were analysed for the presence and location of endocardial fibroelastosis and its possible relationship to pressure, direction, jet-effects, and vibrations of the intracardial blood stream, and to myocardial anoxia. In all, 25 different types of congenital heart disease were investigated, and the sites of endocardial thickening are described and the probable character of the intracardial blood flow discussed. It was found that the endocardial thickening followed the same pattern in various examples of the same type of cardiac malformation. It is suggested that in the majority of cases fibroelastosis can be explained by the force and direction of the intracardiac current of blood, while in a minority of cases—such as, for example, anomalous origin of the left coronary artery from the pulmonary artery—endocardial fibroelastosis appears to be the result of anoxia of heart muscle. [The abstracter would agree with the authors except in their interpretation of that characteristic type of malformation in which an extremely small left ventricle is lined by a thick fibroelastic membrane and associated with hypoplasia of the mitral valve and usually stenosis or obliteration of the aortic ostium. No comparable fibroelastosis is seen in other conditions in which the myocardium is nourished by mixed blood. In the former case an error in the differentiation of the embryonic endomyocardial primordium as the result of faulty nourishment from the ventricular cavity appears to be the most likely explanation.]

In their second paper the authors distinguish fibroelastosis of the left ventricle without cardiac malformation ("primary" fibroelastosis) from other forms of fibroelastic endocardial thickening as a definite disease entity. They describe the clinical features and pathological findings in 17 examples of this disease and review the literature. In the authors' material there were 2 cases of familial incidence, and occurrence in siblings or twins has been reported in the literature on several occasions. In their own series the authors could establish no relation to race, sex, or order of birth, but in the cases collected from the literature there was a marked preponderance of females. They conclude that a genetic defect is the most probable cause of the disease, and suggest this may be a metabolic, possibly an enzymatic, defect. *H. S. Baar*

CHRONIC VALVULAR DISEASE

562. **Mitral Stenosis with Very High Pulmonary Vascular Resistance and Atypical Features**

J. MACKINNON, E. G. WADE, and C. F. H. VICKERS. *British Heart Journal* [*Brit. Heart J.*] **18**, 449–457, Oct., 1956. 5 figs., 12 refs.

In this paper from Manchester Royal Infirmary are described 6 cases with severe (Grade-IV) mitral stenosis accompanied by pronounced pulmonary hypertension. It is pointed out that murmurs may be considerably modified and pathognomonic murmurs may be absent in these cases. In the present series a great increase in pulmonary vascular resistance was the most striking feature. Radiologically, the right ventricle was invariably much enlarged, but enlargement of the left atrium was only slight in 4 and moderate in 2 cases. Once symptoms appeared deterioration was more rapid than in the average case and response to medical treatment poor. Valvotomy was performed in 5 cases, with excellent results in 3 (2 having improved to Grade I and the other to Grade II) and one death; in the remaining case the period of postoperative observation was too short to judge results. Because surgery holds out such good prospects, the importance of the early recognition of this condition, despite the absence of typical murmurs and other common signs, is stressed. *A. Schott*

563. **The Nature of the Increased Pulmonary Vascular Resistance in Mitral Stenosis**

E. G. WADE, J. MACKINNON, and C. F. H. VICKERS. *British Heart Journal* [*Brit. Heart J.*] **18**, 458–466, Oct., 1956. 6 figs., 23 refs.

In an investigation at Manchester Royal Infirmary the effect on circulatory dynamics of hexamethonium (8·5 to 12·5 mg.) injected into the pulmonary artery through a catheter was examined before and after exercise on a bicycle ergometer in 10 cases of mitral stenosis with pulmonary hypertension. In most of these cases the resting mean pulmonary arterial pressure fell; the effect on resting total pulmonary resistance was variable, there being a tendency to fall in 5, a rise in 3, and no change in 2 cases. Exercise produced an increase in pulmonary

resistance in all cases. The effect of hexamethonium on pulmonary resistance after effort was again variable. No relation between the effect of hexamethonium on the resting resistance and the degree of its increase after effort was found. Reasons are given why the results obtained in this study do not support the assumption that the raised pressure is due to autonomic nervous activity. An indirect action of hexamethonium on pulmonary resistance through an effect on capillary venous pressure is put forward by way of explanation, a local reflex, not under autonomic nervous control, being assumed to be the underlying factor. Atropine, given intravenously in doses varying between 1/120 and 1/75 gr. (0·54 and 0·86 mg.) to 8 fully digitalized patients with severe mitral stenosis and auricular fibrillation, had no consistent effect on circulatory dynamics.

A. Schott

564. **A Clinical Study of One Hundred Cases of Severe Aortic Insufficiency**

J. SEGAL, W. P. HARVEY, and C. HUFNAGEL. *American Journal of Medicine* [*Amer. J. Med.*] **21**, 200–210, Aug., 1956. 5 figs., 24 refs.

The natural history and clinical features of severe aortic incompetence are discussed with reference to 100 cases seen at Georgetown University Medical Center, Washington, D.C. The criteria of severity were: (1) loud blowing aortic diastolic murmur; (2) wide pulse pressure with a low diastolic pressure; (3) peripheral signs of aortic incompetence; (4) radiological signs of a rocking motion of the heart and a marked systolic expansion of the aorta; and (5) carotid or other pulse tracings consistent with free aortic incompetence. The condition was rheumatic in origin in 83 of the 100 cases, syphilitic in 12, congenital in 4, and traumatic in one. There were 75 men in the series, but the authors note that of the 8 rheumatic patients with associated mitral stenosis, 6 were women. The average age of the patients in the rheumatic group was 33 years, in the syphilitic group 46 years, and in the congenital group 32 years. A new classification of cardiac disease (four categories) based on the subjective and objective features is outlined; 83 of the 100 patients fell in Groups C and D—that is, the groups with the most severe aortic insufficiency.

In the rheumatic group the average time interval between the first attack of acute rheumatism and the development of significant aortic incompetence was 7 years, the symptom-free period averaged 10 years, and the final period of progressive symptoms varied from 2 months to 30 years. Symptoms were more rapidly progressive in the syphilitic group than in the rheumatic group. Dyspnoea on exertion, paroxysmal nocturnal dyspnoea, palpitations, and angina pectoris were the commonest symptoms; anginal pain occurred in half of the patients in the rheumatic group. All patients with pure aortic incompetence were in sinus rhythm. Bacterial endocarditis occurred in 18 of the 83 patients in the rheumatic group. The authors state that factors indicating a poor prognosis include recent bacterial endocarditis, coexisting angina pectoris and congestive cardiac failure, an enlarged heart, a syphilitic aetiology, and increasing age and duration of symptoms. They do not, however, accept the view that once a patient with aortic incompetence goes into failure the course of the disease is invariably downhill.

J. Warwick Buckler

565. **Aortic Valvulotomy under Direct Vision during Hypothermia**

F. J. LEWIS, N. E. SHUMWAY, S. A. NIAZI, and R. B. BENJAMIN. *Journal of Thoracic Surgery* [*J. thorac. Surg.*] **32**, 481–492, Oct., 1956. 7 figs., 16 refs.

The authors state that there has been some disappointment regarding the results of operations for the relief of aortic stenosis. This, they believe, is because (1) the valve is often heavily calcified and hence cannot be restored to its normal condition, and (2) hitherto the usual methods of operation have been closed ones. They therefore propose that the second objection at least could be obviated if the aorta were opened under hypothermia. In experiments carried out at Ancker Hospital, St. Paul, Minnesota, on dogs they determined the amount of air which could safely be allowed into the coronary and cerebral arterial circulations, and from these experiments, which are fully described, they devised methods whereby the amount of air liable to cause embolism could be reduced to a minimum.

In the clinical application of these results the method of hypothermia was in general that employed by Swan *et al.* (*J. thorac. Surg.*, 1954, **28**, 504; *Abstracts of World Medicine*, 1955, **17**, 276) in their operation for correction of pulmonary stenosis under direct vision. Air was washed out of the left ventricle by perfusion through a catheter in the atrium before the aortic wound was closed. So far this operation has been performed on only 3 patients. Adequate commissurotomy was possible in all 3 cases, although stout scissors had to be used. One patient died as the result of haemorrhage from the aortic wall, but the other 2 made an uneventful recovery and have shown considerable symptomatic improvement.

J. R. Belcher

CORONARY DISEASE AND MYOCARDIAL INFARCTION

566. **A Clinico-pathological Study of Coronary Disease**

P. J. D. SNOW, A. M. JONES, and K. S. DABER. *British Heart Journal* [*Brit. Heart J.*] **18**, 435–441, Oct., 1956. Bibliography.

The pathological findings in 25 cases with clinical evidence of ischaemic heart disease studied at Manchester University have already been described (*Brit. Heart J.*, 1955, **17**, 503; *Abstracts of World Medicine*, 1956, **19**, 340); in the present paper these findings, together with those in 7 additional cases, are correlated with the clinical features. At necropsy the coronary arteries were injected with radio-opaque material and radiographed; the myocardium was then serially sectioned and all lesions examined histologically. Of the 53 coronary occlusions demonstrated, 7 had produced no infarction, and all 7 were in arteries supplying pre-

viously infarcted areas. The number of infarcts found was 77, of which 52 were less than one month old and could be related to the clinical history. Of these 52, 28 (54%) corresponded with attacks of prolonged cardiac pain, 2 (4%) with the onset of angina of effort, 2 (4%) with the onset or aggravation of dyspnoea, and 19 (36%) had given rise to no apparent symptoms; one occurred in a comatose patient. Of the 21 recent infarctions which had occurred without coronary occlusion, 12 (57%) were symptomless, whereas only 7 of 30 occurring with coronary occlusion were asymptomatic. There was no correlation between the symptoms and the size or site of infarcts. It was concluded that cardiac pain lasting more than half an hour is a reliable indication of myocardial infarction. A high proportion of cardiac infarcts give rise to no recognizable symptoms, and the reasons for this are obscure. *C. Bruce Perry*

567. **Geographic Patterns in Deaths from Coronary Heart Disease**

P. E. ENTERLINE and W. H. STEWART. *Public Health Reports* [*Publ. Hlth Rep. (Wash.)*] **71**, 849–855, Sept., 1956. 2 figs., 2 refs.

The data presented in this paper are the age-standardized death rates in the United States from coronary heart disease for the year 1950 (a census year) for white males and females in each of the 48 States and the District of Columbia. These rates are also shown for groups of States forming nine geographical regions of the U.S.A. For each sex a map shows each State classified according to the appropriate quartile of the distribution of the rates. These quartile groups, with 12 States in each, were (in deaths per 100,000): for males, 191·1 to 232·3, 234·3 to 272·5, 274·7 to 303·2, and 304·9 to 393·8; and for females, 83·4 to 105·0, 105·5 to 117·6, 120·9 to 143·7, and 145·7 to 217·4. The rates for each State or region were standardized for age by the direct method, using the 10-year age-specific rates of the particular area and the 1950 census figures for the U.S.A. as the standard population. For males in the nine geographical regions age-specific mortality from all causes and from coronary heart disease are given for the age groups 45–54, 55–64, 65–74, and 75–84 years.

The range of the rates for males shows that in some States the number of deaths attributed to coronary heart disease was almost twice as great as in others. Thus in New Mexico the minimum rate of 191·1 per 100,000 was reported, while the maximum, 393·8 per 100,000, occurred in New York State. Even more striking differences occurred in the rates for females, the minimum being 83·4 per 100,000 in New Mexico and the maximum 217·4 per 100,000 in New York State. Nearly one-third of all male deaths and about a quarter of all female deaths in the age group 45–74 were due to coronary thrombosis. For males in this broad age group there was a positive correlation between the mortality from all causes and that from coronary heart disease in the 9 geographical regions. In fact, in the age group 65–74 coronary heart disease accounted for most of the variation in the mortality from all causes in the different regions. It is stated that similar trends were observed for females.

The authors recognized that the interpretation of their data might be confused by differing standards of diagnosis and different degrees of urbanization in different States, so they tried, perforce indirectly, to find evidence of any such bias in their data, but without success. They conclude that the observed differences represent true geographical variations in the incidence distribution of coronary heart disease, and suggest that studies in aetiology might well be carried out in the areas of high and low mortality from this cause in the U.S.A.

E. A. Cheeseman

568. **Alimentary Lipaemia in Men with Coronary Artery Disease and in Controls**

D. W. BARRITT. *British Medical Journal* [*Brit. med. J.*] **2**, 640–644, Sept. 15, 1956. 4 figs., 17 refs.

At the United Bristol Hospitals the extent of alimentary lipaemia following a fat meal was studied in 35 men recovering from myocardial infarction (without congestive heart failure) and the findings compared with those in an age-matched control group of 33 healthy men and a further control group of 14 healthy premenopausal women. After a fasting sample of venous blood had been taken a standard meal was given, consisting of 4 oz. (114 ml.) of milk and the same amount of thick cream, with cornflakes and a cup of tea, the whole containing about 60 g. of fat. Blood samples were taken 3, 5, and 7 hours after the meal, no further food being allowed until the last sample had been collected. The blood was allowed to clot, the serum separated, and after standing overnight the optical density of each sample was read in a spectrophotometer at 680 millimicrons, while the total serum lipid content was estimated gravimetrically by Bloor's method.

Before the meal the optical density of the serum varied considerably in all three groups, but there was a statistically significant difference between the mean values for the group with coronary disease and for the male controls, the former being higher. A similar difference existed, though it was not significant statistically, 3 hours after the fat meal, and highly significant differences at 5 and 7 hours. While the mean optical density of the sera from the male controls was at all times higher than that of the sera from the female controls, none of these differences reached statistical significance. Furthermore, no clear relationship was found between body weight and duration of lipaemia (though its intensity tended to be a little less in heavier subjects), or between age and either intensity or duration of lipaemia. Limited physical activity did not appear to influence the optical density measurements greatly. The intensity of the lipaemia, however, varied to some extent in the same patient on repeated examination in the same conditions. Chemical estimation of the serum total lipid content showed similar trends, but the findings were unsatisfactory owing to the size of error in the method used.

The results of the present investigations confirm previous reports that there is an increased number of fat particles in the fasting blood and an increase in the

intensity and duration of lipaemia following a fat meal in patients with coronary disease compared with healthy subjects. It is suggested that if this were made the basis of a diagnostic test, a 7-hour reading would give the most reliable results as the difference is then most pronounced. The most likely explanation of the abnormality would seem to be an inability of patients with coronary disease to clear their blood of fat particles, a theory which is supported by the reduced effect of an intravenous injection of heparin on the lipaemia in such cases; the average degree of clearing after such an injection given between 3 and 5 hours after the fat meal in the male control group was 36·4%, and in the coronary group only 14·9%. *Z. A. Leitner*

569. **Prothrombin and Fibrinogen Levels in Myocardial Infarction and Angina Pectoris.** (К вопросу об уровне протромбина и фибриногена при инфаркте миокарда и стенохардии)
V. E. FRADKINA. *Терапевтический Архив* [*Ter. Arkh.*] **28**, 32–39, No. 6, 1956. 2 figs., 12 refs.

After reviewing the Russian and some of the foreign literature on the coagulability of the blood in myocardial infarction the author presents details of the investigation of 50 cases, 30 of myocardial infarction and 20 of angina pectoris, seen at the Botkin Hospital, Moscow. In the acute stage of myocardial infarction, particularly when there is extensive focal necrosis, there is hypoprothrominaemia lasting one to 2 weeks and thereafter a gradual rise in the prothrombin level. In contrast, the plasma fibrinogen content in the acute stage is high and dependent on the extent and severity of the process, while a fall to normal levels occurs simultaneously with the rise in the prothrombin level. When the course of the infarction is protracted (with the production of cardiac aneurysm) the fibrinogen content may remain high for a much longer period (57 days or more). In angina pectoris the plasma prothrombin curve shows a steady rise, but the fibrinogen level remains within normal limits.

It is suggested that prothrombin determinations are valuable in indicating the best time for the administration of anticoagulants, and also that the definite increase in plasma fibrinogen content observed in myocardial infarction could serve as a differential diagnostic feature between this condition and angina. *R. Crawford*

570. **Metalloenzymes and Myocardial Infarction. II. Malic and Lactic Dehydrogenase Activities and Zinc Concentrations in Serum**
W. E. C. WACKER, D. D. ULMER, and B. L. VALLEE. *New England Journal of Medicine* [*New Engl. J. Med.*] **255**, 449–456, Sept. 6, 1956. 5 figs., 24 refs.

Serum lactic and malic dehydrogenase are stable in all human serum studied and readily assayed. Activities for both were elevated 2 to 10 times above those normally observed in all cases of clinically proved myocardial infarction. Serum zinc levels are lowered significantly after acute myocardial infarction. Serum lactic dehydrogenase activity is not elevated in angina pectoris, severe coronary insufficiency and myocardial ischemia.

Although serum lactic dehydrogenase rises in other pathologic states, such as renal necrosis and parenchymal liver disease, it is relatively precise and useful to employ this test for the diagnosis of acute myocardial infarction. —[Authors' summary.]

571. **A Completed Twenty-five-year Follow-up Study of 200 Patients with Myocardial Infarction**
D. W. RICHARDS, E. F. BLAND, and P. D. WHITE. *Journal of Chronic Diseases* [*J. chron. Dis.*] **4**, 415–422, Oct., 1956. 13 refs.

The completed after-history of 200 patients with myocardial infarction, seen in consultation in the decade 1920 to 1930, has been viewed through a 25-year follow-up. Of the entire series, 38 died during the first 4 weeks after the initial attack. Their deaths have been designated "immediate" mortality. Of the remaining 162 patients, 79 (49%) survived 5 years, 50 (31%) survived 10 years, 23 (14%) survived 15 years, and 8 (5%) survived 20 years. Six patients of the 8 surviving 20 years lived for 25 years after their initial myocardial infarction. Two of these patients are alive 28 and 29 years later.

The best index to long-term prognosis following myocardial infarction is the degree of recovery of the patient following the acute period of infarction. Of the 55 patients who had "complete" clinical recovery following myocardial infarction, 45 (82%) were alive after 5 years, 31 (56%) were alive after 10 years, and 6 (11%) were alive after 25 years. The two patients known to be living now, 28 and 29 years after infarction, are of the "complete" recovery group.

Finally, available statistics of past experiences are not as yet complete enough to be fully adequate. Hence, they can form at best only part of the basis for decision in any individual case. No two persons are exactly alike and the physician who practises medicine must base his diagnosis, prognosis, and treatment for the most part on the current findings in the individual case.—[Authors' summary.]

572. **A Completed Twenty-five-year Follow-up Study of 456 Patients with Angina Pectoris**
D. W. RICHARDS, E. F. BLAND, and P. D. WHITE. *Journal of Chronic Diseases* [*J. chron. Dis.*] **4**, 423–433, Oct., 1956. 6 figs., 14 refs.

A completed 25-year follow-up study has been made of 456 patients with angina pectoris resulting from coronary atherosclerosis observed during the period 1920 to 1931. Of the 456 patients with angina pectoris, 445 are dead, 6 are still living, and 5 have been lost to follow-up. The average duration of survival in the 445 patients who have succumbed was 9·4 years. The 6 living patients have survived an average of 31·7 years. The average survival in living and dead patients was 9·7 years. Seventy-six per cent of the deaths were due to cardiac causes. Approximately one-fifth of the entire group had normal cardiac findings, blood pressure, and electrocardiogram at the time of the first examination, and these patients, as a rule, lived longer than the others. Such factors as hypertension, myocardial infarction,

cardiac enlargement, and abnormal electrocardiogram occurred more frequently in patients who died early in the course of their disease than in those surviving longer periods.

In comparing the ratio of observed survival in patients with angina pectoris to the expected survival of the unselected U.S. population, the following points are evident: (*a*) angina pectoris imposes a continuous excess mortality load on patients, which is essentially constant during the entire period of observation; (*b*) this excess mortality is greater in males, of whom some 7% die annually, in addition to the over-all expected mortality; for females, the figure is 5·3%; (*c*) the excess mortality does not differ between a younger and an older group of patients.

These studies, as well as the results of survival rates in the literature of recent years, indicate a more hopeful outlook for patients with angina pectoris than was formerly recognized.—[Authors' summary.]

573. **Follow-up Report on Resection of the Anginal Pathway in Thirty-three Patients**

C. F. BURNETT and J. A. EVANS. *Journal of the American Medical Association* [*J. Amer. med. Ass.*] **162**, 709–712, Oct. 20, 1956. 1 fig., 2 refs.

The results of sympathectomy in 33 patients with angina pectoris with or without hypertension are reported from the Lahey Clinic, Boston, unilateral or bilateral sympathectomy being carried out at various levels from the third lumbar to the inferior cervical ganglion. There were 3 operative deaths and 6 during a follow-up period of 16 months to 7 years. The response to operation varied widely; in some cases it was dramatic and in some definite but temporary. Occasionally unilateral sympathectomy gave relief. In one case in which the unilateral operation was unsuccessful there was relief of pain with subsequent contralateral resection. Of the 30 patients surviving operation, 18 had complete relief from anginal pain for one to 11 years.

Discussing the failure in 8 cases to obtain immediate or permanent relief the authors state that 2 of the patients had complete relief for several months until cardiac infarction recurred, while a third later obtained relief from a second, more complete, resection of the sympathetic chain. In 2 the pathway was resected on one side only, but in one of these there was complete relief when resection was later performed on the other side. Only the first and second thoracic ganglia on the left were resected in one case, and in one there was regrowth of sympathetic fibres. The authors state that 3 failures "were marked by an emotional overlay; in 2 of these the diagnosis of true angina was questionable". Coronary infarction subsequently occurred in 5 of the 8 cases, with one death.

It is concluded that sympathectomy affords relief to certain selected patients with disabling angina pectoris, the best results being obtained in those with hypertension, "especially when the procedure is combined with extensive sympathectomy and splanchnicectomy. It is also of benefit to the patient with the overalarm type of anginal pain, provided emotional overlay can be eliminated". *J. V. Crawford*

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574. **The Treatment of Angina Pectoris with Visnagane.** (Le traitement de l'angine de poitrine par le visnagane)

J. MONIZ DE BETTENCOURT, A. CORREIA RALHA, F. PERES GOMES, and H. PRISTA MONTEIRO. *Presse médicale* [*Presse méd.*] **64**, 1468–1470, Sept. 8, 1956. 2 figs., 17 refs.

The authors, using their own method, have isolated from the fruit of the plant *Ammi visnaga* a pure, crystalline substance known as visnagane, and in this paper from Lisbon describe the results of chemical, pharmacological, and clinical studies made with the new substance. Chemically, visnagane is allied to coumarin. Pharmacological tests on various species of experimental animal showed it to be a coronary vasodilator and a relaxant of smooth muscle with an action some 6 to 9 times greater than that of khellin. Its experimental toxicity in the rat was minimal. In human subjects oral administration of visnagane was well tolerated and caused no digestive disturbance. Intramuscular injections were painless and laboratory examination of the blood and urine carried out during treatment showed no abnormalities.

Of 35 patients who were studied clinically, 3 had had acute coronary thrombosis, 4 aortic regurgitation, and the remainder were suffering from angina due to coronary sclerosis. After a period of placebo administration visnagane was given in doses of 20 to 200 mg. per day for periods up to one year. The effects of this therapy, as evaluated by the reported subjective improvement, increase in exercise tolerance, and improvement in the electrocardiogram, were considered satisfactory; in particular, within a week of the beginning of treatment the patients noted a diminution in the frequency and severity of attacks of angina.

In the authors' opinion visnagane is a more efficient coronary vasodilator than khellin or aminophylline [though no systematic comparative studies were made] and has the added advantage of lesser toxicity.

Marcel Malden

BLOOD VESSELS

575. **Contribution to the Aetiology of Atherosclerosis.** (Материалы к этиологии атеросклероза)

M. I. GESSE and B. V. IL'INSKIĬ. *Терапевтический Архив* [*Ter. Arkh.*] **28**, 17–27, No. 6, 1956. 2 figs.

At the First (Pavlov) Medical Institute, Leningrad, special anamnestic records, giving details of factors possibly concerned in the causation of atherosclerosis—such as temperament, occupation, physical labour and strains, fatigue, psychical trauma, food habits (particularly the intake of animal protein and lipids), alcohol, smoking, past illnesses, sexual life, blood pressure, and heredity—and their operation during the various periods of life, were prepared for 144 patients who came to necropsy [for reasons unstated], and these were studied in relation to the pathological findings in the arteries.

In general a correlation was found to exist between the amount of lipid, particularly cholesterol, in the diet and atherosclerotic changes in the intima of the arteries, prolonged and regular consumption of large quantities of lipids being associated with progressive atherosclerosis,

recent excess lipid consumption with lipid infiltration of the intima not of clinical significance, and earlier but irregular heavy consumption with the finding of plaques in the intima. In cases in which there were atherosclerotic changes despite moderate or low lipid consumption, the changes are ascribed to endogenous disturbance of cholesterol or lipid metabolism, prolonged hypertension, or to local inflammatory changes in the arterial walls, these being regarded as subsidiary factors in the production of atherosclerosis. Reference is also made to factors which possibly counteract the development of atherosclerosis (namely, vitamin C, choline, thyroid extract, and insulin) and to the unknown effect of physical factors, such as exertion and climate.

R. Crawford

576. **The Course and Prognosis of Coarctation of the Aorta**

M. CAMPBELL and J. H. BAYLIS. *British Heart Journal* [*Brit. Heart J.*] **18**, 475–495, Oct., 1956. 10 figs., bibliography.

At Guy's Hospital and the Institute of Cardiology, London, the course of and prognosis in coarctation of the aorta were studied in a series of 130 cases, 80 of which were followed up for an average period of 5 years. Aortic stenosis was present in 6 and aortic regurgitation in 28. Altogether 16 patients died, 6 in the third decade, unexpectedly. After discussing the incidence, sex and age distribution, and the more important diagnostic features of coarctation of the aorta, the authors describe the course of the disease as seen in each decade of life.

Of 28 patients in the first decade, 3 died; most of the remainder were well and leading a normal life without symptoms, although generally the blood pressure showed a steady increase. There were 50 patients in the second decade, one of whom died. In most cases this decade was uneventful, although the blood pressure continued to rise. Cerebrovascular attacks occurred in 4 patients in this age group. Of 37 patients in the third decade, 5 died " rather suddenly within 2 or 3 years of a time when they seemed as well as ever ". The blood pressure at this age was steady, and many of the patients still considered that they were symptomless although headaches were more frequent. There were 17 patients in the fourth decade; of the 2 who died, one had aortic regurgitation and one aortic stenosis. The oldest patient in the series was first seen at the age of 52; she died 3 years later in congestive cardiac failure. The authors state that blood pressure rises with age, the systolic much more than the diastolic—55 mm. Hg as against 20 mm. Hg from 5 to 40 years of age—the rise being steep until the age of 17. The main causes of death in patients with coarctation of the aorta are discussed, including rupture of the aorta, intracranial haemorrhage, bacterial endocarditis and aortitis, and congestive heart failure.

The authors advise surgical treatment for most children and state that after the age of 8 this should not be delayed, especially in the presence of aortic regurgitation. Of 46 patients operated on during the last 6 years, 7 died. The results of surgical treatment in the authors' cases were generally good. On the average the systolic pressure fell about 40 mm. Hg and the diastolic pressure about 20 mm. Hg. Patients with disabling symptoms were much improved. The electrocardiogram showed that signs of left ventricular strain were lessened after successful operation, and in 6 cases were almost or completely abolished.

A. I. Suchett-Kaye

SYSTEMIC CIRCULATORY DISORDERS

577. **Paravertebral Procaine Blockade in the Treatment of Hypertensive Disease.** (Опыт лечения больных гипертонической болезнью паравертебральной новокаиновой блокадой)

N. M. DAVŸDOV. *Терапевтический Архив* [*Ter. Arkh.*] **28**, 60–62, No. 6, 1956.

In the treatment of hypertensive disease bilateral blockade (four injections each of 25 ml. of 0·25% procaine) at the level of T1 to T4 in the region of the stellate ganglion was performed on 142 patients with hypertension, 38 of whom were in the neurogenous labile stage, 101 in the transitional stage, and 3 with arteriosclerotic changes in the kidneys. In most cases the block was repeated (in some cases twice) at intervals of 4 or 5 days. Patients with advanced disease did not respond, but most of the others were relieved of symptoms and showed a fall in blood pressure; at follow-up examination 60% of them were pronounced fit for work. To prevent recurrence the patients attend a local polyclinic where the treatment is repeated twice a year.

R. Crawford

578. **Evaluation of Hydralazine (" Apresoline ") in Fixed Hypertension**

E. J. DRENICK and G. M. KALMANSON. *Angiology* [*Angiology*] **7**, 368–377, Aug., 1956. 14 refs.

The authors review the literature on the value of hydrallazine in the treatment of hypertension. They consider that the hypotensive effect of the drug is due to central inhibition of sympathetic pressor impulses [but they offer no evidence in support of this view]. At the Veterans Administration Center, Los Angeles, hydrallazine was given to 38 out of 300 long-stay patients in whom hypertension had previously been diagnosed, patients with angina pectoris, recent myocardial infarction, cerebrovascular disease, or renal disease causing uraemia being excluded from the trial. In general only those with a diastolic pressure above 100 mm. Hg in barbiturate-induced sleep were included. The dosage of hydrallazine was 200 to 800 mg. daily. Those patients who did not respond satisfactorily were given hexamethonium in addition.

An excellent response, which was defined as a waking diastolic pressure consistently below 100 mm. Hg, was observed in 12 patients, 2 of whom required hexamethonium also; in 4 other patients there was a good response but treatment had to be stopped because of side-effects; the response was inconstant in 3 patients and inadequate in 7, while in the remaining 12 patients treatment was discontinued because of side-effects. The

drug was temporarily replaced by a placebo in a few cases in order to ensure that the results of treatment were not psychological.

Headaches and dizziness were the commonest toxic effects, but these often cleared when the higher doses were reached; less common were drowsiness, nausea, paraesthesiae, constipation, and retention of urine. There was evidence of decreased cardiac reserve in 10 patients. *D. Goldman*

579. **The Hypotensive Action of Mecamylamine**
A. E. Doyle, E. A. Murphy, and G. H. Neilson. *British Medical Journal* [*Brit. med. J.*] **2**, 1209–1211, Nov. 24, 1956. 1 fig., 9 refs.

This is a report from the Postgraduate Medical School (Hammersmith Hospital), London, of a preliminary trial of the hypotensive effects of mecamylamine when given by mouth. This drug, a ganglion-blocking secondary amine reputed to be fully absorbed from the alimentary tract, is compared with pentolinium (given subcutaneously and, in some cases, orally) in its control of blood pressure (recorded standing) in 45 hypertensive patients. Of these, 25 were treated for 6 to 10 months, 15 for 3 to 6 months, and the remaining 5 discontinued treatment within one month of starting. Mecamylamine by mouth caused a more prolonged and smoother fall in blood pressure—lasting about 12 hours and starting about one hour after administration—than an equally effective oral or subcutaneous dose of pentolinium, and no tolerance to the drug was found. Side-effects from parasympathetic block, particularly constipation, were common with mecamylamine, but no greater than with pentolinium. Of the 45 patients, 24 had good blood-pressure control with negligible side-effects, in 12 the latter were severe, and in 9 they precluded control.

The suggested dosage scheme for mecamylamine was two equal oral doses at 12-hour intervals, starting with not more than 2·5 mg. twice daily and adding increments of 2·5 mg. not more frequently than at 3-day intervals until the blood pressure was adequately controlled. This was practicable in out-patients providing standing blood-pressure measurements over several hours could be obtained; most cases required between 10 and 25 mg. twice daily. The authors conclude that in spite of side-effects the advantages of oral administration, prolonged hypotensive action, and predictability of response make mecamylamine the most reliable hypotensive agent yet available. *P. Hugh-Jones*

580. **The Effects of Reserpine on Hypertensive Patients over a Period of Two Years**
R. Hodgkinson. *British Heart Journal* [*Brit. Heart J.*] **18**, 523–528, Oct., 1956. 2 figs., 11 refs.

The author set out to assess the value of reserpine in the treatment of hypertension, stating that his criteria in judging such a drug are its ability to reduce the diastolic and systolic blood pressures by 20 mm. Hg or more throughout the day, combined with an absence of development of tolerance to its action, an absence of toxicity, and an absence of side-effects likely to interfere with the patients' ability to work and enjoy life. In this paper he describes a clinical trial which was carried out on 34 hypertensive out-patients at the West Middlesex Hospital, Isleworth, over a period of 2 years. The patients' mean blood pressure was 150/100 mm. Hg or higher and all were able to attend at least once a month. The procedure was as follows. Inert tablets were given for 6 to 9 months, then tablets of reserpine in a dose of 1 to 2 mg. daily for 12 months, and finally the patients were divided into two groups, one of which received reserpine and the other inert tablets for a further 3 to 6 months. The blood-pressure readings were all taken as far as possible under identical conditions by the same physician and symptoms were assessed at regular intervals throughout the trial, which was completed by 33 of the 34 patients.

The average reduction in blood pressure following administration of reserpine was 18 mm. Hg systolic and 15 mm. Hg diastolic, 14 (40%) of the patients showing a reduction of 20 mm. Hg or more in both systolic and diastolic pressures. Tolerance to reserpine did not develop in any patient over the entire period of administration. One-third of the patients described a feeling of calmness and well-being, which was partly offset, however, by a feeling of tiredness, depression, and loss of initiative. One patient, a man aged 54, had to be excluded from the trial because of extreme depression after 3 months' treatment. It is concluded that the use of reserpine is justified in certain hypertensive patients, but the author recommends that the physician should be on the alert for signs of lassitude, depression, or other mental disturbances, which may contraindicate use of the drug. *Joan Yell*

581. **Hypertension Treated with *Rauwolfia canescens*: a Comparison with *Rauwolfia serpentina***
R. W. P. Achor and N. O. Hanson. *New England Journal of Medicine* [*New Engl. J. Med.*] **255**, 646–650, Oct. 4, 1956. 15 refs.

A trial of a preparation of the whole root of *Rauwolfia canescens* in the treatment of hypertension is reported. Of the many alkaloids of *R. canescens*, at least three are known to possess hypotensive activity—rauwolscine, reserpine, and 11-desmethoxyreserpine. At the Mayo Clinic 19 patients with moderate hypertension were given a placebo for 3 months and then 400 mg. of the preparation of *R. canescens* daily for 2 months. Blood pressure was recorded weekly in standard conditions. The average blood pressure when the placebo was being given was 185 mm. Hg systolic and 110 mm. Hg diastolic. After administration of the drug the readings were 163 and 98 mm. Hg respectively. In a previous trial (Achor *et al.*, *J. Amer. med. Ass.*, 1955, **159**, 841) the average blood pressure of the same group of patients during treatment with a preparation of *R. serpentina* was 168 mm. Hg systolic and 98 mm. Hg diastolic.

In a second part of the present investigation administration of *R. canescens* was continued for 6 or 8 months. After 5 months the dose in 12 patients was reduced to 200 mg. daily without diminishing the hypotensive effect; in 5 others who had responded poorly to a daily dose of 400 mg. an increase to 600 mg. daily did not result in

any improvement in the response. In many patients *R. canescens* caused bradycardia, nasal congestion, abdominal cramps, and diarrhoea; other side-effects were an increase in appetite and gain in weight. These side-effects were less troublesome than those experienced by the same patients given *R. serpentina* in a dosage of 400 mg. daily. The sedative effect of *R. canescens* was less than that of *R. serpentina*; only one patient receiving the former drug experienced a mild transient depressive episode. Clinical improvement was noted after treatment in nearly all patients.

Bernard Isaacs

582. **Circulation in the Hands in Hypertension**
R. S. DUFF. *British Medical Journal* [*Brit. med. J.*] **2**, 974–976, Oct. 27, 1956. 2 figs., 13 refs.

The resting levels of blood flow in the hands of 36 healthy and 25 hypertensive subjects were measured by venous occlusion plethysmography under standard conditions. In the healthy subjects the blood flow varied widely between different individuals, but averaged 10·5 ml. per 100 ml. hand volume per minute for the entire group. In the hypertensive patients the level of hand blood flow tended to be inversely related to the height of the diastolic arterial pressure; in those with mild hypertension the flow was on average higher than in the healthy subjects, while in those with severe hypertension the hand flow was much below normal. The results are interpreted as evidence that in hypertension a *functional* abnormality of the vessels themselves is probably more important than excessive activity of the vasomotor nerves. —[Author's summary.]

583. **Telangiectasia in Raynaud's Disease**
D. VEREL. *Lancet* [*Lancet*] **2**, 914–917, Nov. 3, 1956. 6 figs., 10 refs.

In this paper from Guy's Hospital, London, is described a study of the capillary blood vessels in Raynaud's disease. A binocular dissecting microscope was used and the skin illuminated by a heat-filtered lamp. The skin was first cleared with liquid paraffin and a suitable spot selected. The point of a fine needle was gently pressed until it penetrated the epidermis; it was then withdrawn and the paraffin wiped off the skin. A drop of adrenaline in 1:1,000 aqueous solution was then placed on the hole made and the effect of the drug on the capillaries studied. The experiment was then repeated with freshly prepared histamine in 1:3,000 aqueous solution. The clinical material consisted of 9 women (aged from 39 to 66 years) with Raynaud's disease of 10 years' duration or longer, 7 of whom had trophic changes in the skin and 2 had subcutaneous deposits of calcium in the fingers; in no case was there evidence of scleroderma.

In all cases telangiectases were found consisting of dilated vessels covering irregular areas ranging in size from 0·5 mm. square to 8 mm. square, the colour varying from blue to bright red according to the skin temperature. Lesions were present on the lips, hands, forehead, nose, and cheeks, and occasionally on the forearms. Lesions were constantly present on the lips, where they would extend from the mucosa to the surrounding skin without any change in character at the junction. Microscopically, a typical lesion showed a complex network of vessels up to 0·12 mm. in diameter, which under higher magnification was seen to be dilated venules of the subcapillary venous plexus.

Light touch on the skin overlying a telangiectatic area caused immediate dilatation of the abnormal vessels, whereas adrenaline introduced through a prick led to profound vasoconstriction; when histamine was used in the same way slight dilatation of the vessels occurred. Thus it is apparent that the vessels in Raynaud's disease retain their normal contractility. It is suggested that this response to local stimulation serves to differentiate the telangiectases seen in Raynaud's disease from all other forms of telangiectasia, which do not so respond. No definite conclusions were formed as to the nature of the lesions in Raynaud's disease. *I. McLean Baird*

PULMONARY CIRCULATION

584. **Hypertensive Pulmonary Vascular Disease**
D. HEATH and W. WHITAKER. *Circulation* [*Circulation (N.Y.)*] **14**, 323–343, Sept., 1956. 22 figs., bibliography.

The purpose of this paper from the Royal Hospital, Sheffield, is " to describe the clinical and histological features . . . of severe pulmonary hypertension and to define hypertensive pulmonary vascular disease as a distinct clinicopathologic entity ". Six illustrative case histories are presented in which the underlying conditions were: ventricular septal defect, Eisenmenger complex, patent ductus arteriosus, atrial septal defect, mitral stenosis, and primary pulmonary hypertension.

The characteristic symptoms of hypertensive pulmonary vascular disease are dyspnoea, cyanosis, respiratory infections, anginal pain (probably from pulmonary arterial distension), haemoptysis, hoarseness from pressure on the laryngeal nerve, and ultimately congestive heart failure. Physical signs are those of right ventricular hypertrophy, accentuation of the pulmonary second sound, sometimes pulmonary valvular incompetence, and a venous " a " wave in the neck. The electrocardiogram is that of right ventricular hypertrophy, sometimes with incomplete right bundle-branch block, or big P waves from atrial hypertrophy. Radiological examination shows dilatation of the main pulmonary arteries and characteristic decrease in arterial markings in the peripheral lung fields. Findings on angiocardiography and cardiac catheterization are described. Histological examination of the lungs shows a distinctly muscular media in pulmonary arterioles (under 100 μ diameter) and medial hypertrophy in bigger arteries. With severe pulmonary hypertension there is proliferation of the intima, sometimes causing arterial occlusion, and where pulmonary arterial pressure is believed to have risen rapidly there may be medial necrosis in the walls of the arteries. Bigger (elastic) pulmonary arteries may have atheromatous plaques in their intima. Theories of the genesis of pulmonary hypertension are reviewed.

J. A. Cosh

Haematology

585. **"Despeciated" Plasma and the Coagulability of the Blood.** (Plasma despécifié et coagulabilité sanguine) J. KLEPPING and M. TANCHE. *Presse médicale* [*Presse méd.*] **64**, 1493–1494, Sept. 15, 1956. 1 fig.

At the Institute of Physiology, Lyons, the authors have sought to determine whether or not "despeciated" bovine plasma modifies the coagulability of canine blood. Citrated bovine blood was centrifuged, the plasma oxidized with "perhydrol" (a preparation of hydrogen peroxide) and then formolized. The *p*H was adjusted to 7·2 and the plasma heated to 100° C. for 1 hour and finally subjected to Seitz filtration. The injection of this plasma into the veins of dogs affected the coagulation of canine blood, the effect occurring in two phases. In the first phase the immediate effect was a prolongation of clotting time. In the second, delayed, phase the blood was rendered virtually incoagulable, this effect reaching its maximum in 24 hours and then gradually diminishing, to disappear in 48 to 60 hours. The cause of the disturbance of coagulability of the blood is not clear.

Kate Maunsell

HAEMORRHAGIC DISEASES

586. **Vascular Hemophilia. A Familial Hemorrhagic Disease in Males and Females Characterized by Combined Antihemophilic Globulin Deficiency and Vascular Abnormality**
I. SCHULMAN, C. H. SMITH, M. ERLANDSON, E. FORT, and R. E. LEE. *Pediatrics* [*Pediatrics*] **18**, 347–361, Sept., 1956. 10 figs., 35 refs.

The condition known as von Willebrand's disease has until recently been defined as a constitutional haemorrhagic state occurring in either sex, probably transmitted as a Mendelian dominant, and having as its main characteristic a prolongation of the bleeding time. In this paper from New York Hospital–Cornell Medical Center, New York, the authors point out that the term von Willebrand's disease has in the past probably been applied to a variety of conditions. One feature suggesting this is that occasionally, in addition to the prolonged bleeding time, reports have referred to an accompanying coagulation disturbance, the prothrombin consumption being defective.

The authors have studied the coagulation and vascular aspects of 7 cases of the disorder in children, of whom 6 showed a severe disturbance of blood coagulation as revealed by defective prothrombin consumption. It was shown that the thromboplastin defect was a deficiency of antihaemophilic globulin, this being established by the inability of the patient's plasma to correct the defective thromboplastin formation of adsorbed haemophilic plasma in the thromboplastin generation technique, and confirmed by its inability to correct the defective prothrombin consumption of haemophilic blood. [For technical details the original should be consulted.] The inheritance of this deficiency of antihaemophilic globulin is distinct from that of classic haemophilia, in which it is of the sex-linked recessive type. The 7th patient studied had no disturbance of coagulation and showed only a prolongation of the bleeding time.

Study of the vessel pattern in the nail beds and conjunctivae of these patients revealed that this was abnormal in all the cases, including the patient with a normal clotting system. The authors conclude that von Willebrand's disease consists of at least two conditions: (1) a vascular defect plus antihaemophilic globulin deficiency (called by them "vascular haemophilia") and (2) a vascular defect and a normal coagulation mechanism (which they term "pseudohaemophilia").

[This is a very valuable contribution to our knowledge of this disorder.] *A. S. Douglas*

ANAEMIA

587. **A Specific Chemical Difference between the Globins of Normal Human and Sickle-cell Anaemia Haemoglobin**
V. M. INGRAM. *Nature* [*Nature* (*Lond.*)] **178**, 792–794, Oct. 13, 1956. 2 figs., 13 refs.

Although it is well known that normal adult haemoglobin (haemoglobin A) and sickle-cell haemoglobin (haemoglobin S) differ in their electrophoretic properties and in their solubility when in the reduced state, little is known about their chemical differences. The amino-acid composition of the two forms appears to be the same, but it is not known whether the difference between them is due to a different sequence of amino-acids in the polypeptide chains, or to a different folding of otherwise identical chains leading to a masking of some amino-acid side-chains in one form which are accessible in the other. Haemoglobin has too large a molecule for determination of the amino-acid sequences. The author, working at the University of Cambridge, therefore prepared a tryptic digest of each of the two haemoglobins, which should give about thirty peptides with an average chain length of ten amino-acids. These were examined by paper electrophoresis at *p*H 6·4 followed by chromatography with *n*-butyl alcohol, acetic acid, and water, the direction being at a right angle to that of the electrophoretic migration.

Most of the peptides were well resolved and appeared similar in the two proteins. One peptide, however, was neutral on paper electrophoresis at *p*H 6·4 in the haemoglobin-A digest, but migrated towards the negative pole in the haemoglobin-S digest. The same peptide also differed in chromatographic value in the two digests. Thus there would appear to be a difference in the amino-

acid sequence in one small part of one of the polypeptide chains forming the molecules of the two haemoglobin variants. *H. Lehmann*

588. **Haemoglobin C Disease and Trait. Report of a Family in England with Haemoglobin C**
H. M. RICE. *British Medical Journal* [*Brit. med. J.*] **1**, 25–27, Jan. 5, 1957. 3 figs., 9 refs.

589. **An Association between Blood Group A and Pernicious Anaemia**
A COLLECTIVE SERIES FROM A NUMBER OF CENTRES. *British Medical Journal* [*Brit. med. J.*] **2**, 723–724, Sept. 29, 1956. 7 refs.

The combination of data from a number of centres shows with fairly high significance that pernicious anaemia is commoner in persons of Group A than in persons of Group O, and also perhaps, though the numbers are small, than in persons of Group B. The greater incidence in Group A appears in both sexes.—[Authors' summary.]

590. **Studies on the Vitamin B_{12}-binding Principle and Other Biocolloids of Human Gastric Juice.** [In English]
R. GRÄSBECK. *Acta medica Scandinavica* [*Acta med. scand.*] **154**, Suppl. 314, 1–87, 1956. 12 figs., bibliography.

591. **Paroxysmal Nocturnal Hemoglobinuria. Relationship of *in vitro* and *in vivo* Hemolysis to Clinical Severity**
C. F. HINZ, R. WEISMAN, and T. H. HURLEY. *Journal of Laboratory and Clinical Medicine* [*J. Lab. clin. Med.*] **48**, 495–510, Oct., 1956. 4 figs., 21 refs.

Factors influencing the severity and clinical course of paroxysmal nocturnal haemoglobinuria were studied in 3 patients suffering from the disease at the University Hospitals, Cleveland, Ohio. Although the degree of anaemia was similar in the 3 patients, the rate of haemolysis as demonstrated clinically by transfusion requirements and by quantitative studies *in vitro* varied considerably. The most seriously affected patient, a negro woman aged 41 who had had many crises with continuous haemoglobinuria, needed frequent transfusions. Study of erythrocyte survival by means of the radioactive chromium technique showed that in this case 90% of the cells underwent lysis within 3 days. The second patient, a white man aged 39, was less severely affected; he rarely had haemoglobinuria and had received only 18 transfusions in 6 years. In this case the half-survival time of erythrocytes was 8 days (normal, 28 to 35 days). The third patient, a boy aged 9, was only mildly affected and had had one crisis only, following mumps. The half-survival time of erythrocytes in this case was 17 days. The reticulocyte counts in these 3 cases—49%, 13%, and 4%, respectively—accurately reflected the intensity of haemolysis. As the authors point out, the case of the boy is remarkable, for not only is paroxysmal nocturnal haemoglobinuria infrequent in childhood, but in this particular instance the erythrocyte abnormality ultimately disappeared, as judged by tests *in vitro*—a very rare event in the natural history of the disease.

The results of studies *in vivo* in each case were typical of paroxysmal nocturnal haemoglobinuria. Attempts were made by serial studies in the most severe case to determine whether an alteration in the susceptibility of the erythrocytes to haemolysis or in the haemolytic activity of the patient's serum *in vitro* was correlated with the changes in the clinical state from crisis to remission which frequently followed transfusion. Although the patient's serum appeared to be slightly less active *in vitro* in remission than in crisis, this did not seem to provide an adequate explanation for remission, nor did a diminution in the number of susceptible cells. In fact, in this patient in a remission following transfusion the number of susceptible cells rapidly increased without recurrence of crisis. The authors conclude that the mechanism of remission following transfusion cannot yet be satisfactorily explained. *J. V. Dacie*

592. **Reticulocytopenia in Autoimmune Hemolytic Anemia**
W. H. CROSBY and H. RAPPAPORT. *Blood* [*Blood*] **11**, 929–936, Oct., 1956. 5 figs., 4 refs.

Haemolytic syndromes are usually accompanied by a reticulosis, the degree of which is often a good indication of the severity of the haemolysis. Important exceptions to this generalization are pernicious anaemia and also the aplastic crises which may occur in patients with chronic haemolytic anaemia of various kinds, such as hereditary spherocytosis and auto-immune haemolytic anaemia (A.H.A.), and in cases of obliteration of bone marrow by neoplastic or fibrous tissue, when haemolytic disease and reticulocytopenia may occur together. In this study of 57 cases of A.H.A., reported from the Armed Forces Institute of Pathology, Washington, D.C., the reticulocyte response was determined by the reticulocyte count in relation to the patient's haemoglobin level. Of the 57 patients, 34 had idiopathic A.H.A., 15 of them having a relative reticulocytopenia during haemolytic crises; only 3 of the 15 survived, and in all the marrow was hyperplastic. In 16 patients the A.H.A. was secondary to lymphoma, and 10 of these had reticulocytopenia; in the remaining 7 patients the A.H.A. was secondary to lupus erythematosus, infectious mononucleosis, sarcoidosis, or Felty's syndrome, and reticulocytopenia was present in 2. Thus 27 (47·4%) of the patients had a relative reticulocytopenia during haemolytic crises; the mortality in this group was significantly higher than in the cases showing a reticulocytosis. In the cases of idiopathic A.H.A. death was apparently due to the disease process itself, and 18 (53%) of these patients died. Of the patients showing a reticulocytosis, 31·6% died, whereas of the group with reticulocytopenia, 80% died.

The authors stress the erythroid hyperplasia of the marrow in this last group and postulate several reasons for the apparently ominous association of reticulocytopenia and erythroid hyperplasia; the latter varies from inhibition of erythropoeisis to asynchronous maturation of cytoplasm and nucleus of the erythroblasts, active erythrophagocytosis in the marrow, selective action against the reticulocytes by the auto-immune mechanism,

and delayed release of erythrocytes from the marrow. All these mechanisms interfere with the "reticulocyte pool" in the bone marrow. It is suggested that the disease process was most severe in patients who could not produce a reticulocytosis in response to the anaemia.

M. Kendal

593. **Congenital Nonspherocytic Hemolytic Anemia. Two Nonfamilial Cases with Red Cell Survival Studies**
W. KRIVITT, R. T. SMITH, J. F. MARVIN, R. READ, and R. A. GOOD. *Journal of Pediatrics* [*J. Pediat.*] 49, 245–255, Sept., 1956. 6 figs., 13 refs.

From the University of Minnesota Hospitals, Minneapolis, the authors report 2 cases of haemolytic anaemia occurring in children and characterized by macrocytosis, basophilic stippling, hepatosplenomegaly, and jaundice. Using appropriate haematological tests they differentiated the condition from thalassaemia, the sickle-cell trait, and acquired haemolytic anaemia. Although in most of the cases hitherto reported a hereditary tendency was noted, none was found in the 2 cases described here.

In both cases the survival time of erythrocytes labelled with radioactive chromium (^{51}Cr) was studied after transfusion into a normal recipient. The half-life of the labelled cells was 9 and 6 days respectively, compared with 25 to 30 days for healthy cells. It is suggested that this much-reduced life cycle indicates an intracorpuscular defect. When normal erythrocytes labelled with radioactive ^{51}Cr were transfused into the affected patients the half-life was slightly shorter than that of normal erythrocytes in healthy subjects. This, the authors conclude, indicates that an extracorpuscular haemolytic factor was operative as well.

A study of these cases and others reported in the literature showed that macrocytosis is a common feature of this type of haemolytic disease.

D. G. Adamson

NEOPLASTIC DISEASES

594. **Incidence of the Common Forms of Human Leukemia**
B. MACMAHON and D. CLARK. *Blood* [*Blood*] 11, 871–881, Oct., 1956. 3 figs., 17 refs.

From hospital records and from death certificates, an attempt was made to assemble data on all residents of the Borough of Brooklyn diagnosed as having leukemia in the period 1943–52. A total of 1,792 abstracts of hospital records and 1,830 death certificates gave information on 1,709 patients. The mean Brooklyn population over the same period is used to express incidences of the various forms of leukemia in relation to color, sex and age. The incidence of leukemia in white males and females was 71·3 and 57·7 per million per annum respectively. Corresponding rates for Negroes were 46·5 and 30·6. The white–Negro difference was decreased but not eliminated by standardization to allow for differences in the age distributions of the two populations. Sex ratios were lower for the acute forms of the disease than for the chronic forms, and, in both acute and chronic forms, for myeloid than for lymphatic cell types. No relationship of sex ratio with age at diagnosis or initial white cell count was found.

Each pathologic variety of leukemia has its own distinct age incidence curve. The lymphatic forms appear to be more sharply associated with the extremes of life than do the myeloid varieties. That is, acute lymphatic leukemia appears at a younger age than does acute myeloid leukemia and the chronic lymphatic form appears at an older average age than the chronic myeloid variety.—[Authors' summary.]

595. **Acute Leukemia over the Age of Fifty: a Study of Its Incidence and Natural History**
F. W. GUNZ and R. F. HOUGH. *Blood* [*Blood*] 11, 882–901, Oct., 1956. 18 refs.

The analysis of recent reports from 15 different countries for the period 1950–2 has shown that there has been an increase in the incidence of leukaemia, and that this increase has been most marked in persons over the age of 50. The increase among elderly people appears to be absolute, whereas that in children may be due to improved diagnosis. The authors have therefore investigated the incidence of leukaemia in New Zealand and when possible classified the disease according to cell type and degree of chronicity or acuteness. For this purpose the death certificates of 553 persons (316 males and 237 females) certified as dying from leukaemia in the 5-year period 1950–4, for which period the number and composition of the general population of New Zealand was accurately known, were examined; this number represented a mean death rate for the period studied of 10·1 for males and 6·6 for females per 100,000 of the population. The authors think that these figures probably slightly underestimate the true incidence of the disease, chiefly through failure to diagnose acute leukaemia.

Classification of 98·7% of the cases into acute and chronic types was possible from the information on the death certificate; the few subacute cases were included in the acute group, and cases not classifiable from the data on the certificate were placed in the acute group if the duration of the illness had been less than one year and in the chronic group if it had lasted over one year. Classification was little influenced by cell type, and it was assumed that all cases had been adequately investigated pathologically. Distribution by age showed that 20% of cases occurred in the age group 0–15 (12·6% in the 0–5 year age group), 22·9% in the age group 16–50, and 57·1% in the age group 50+. The age distribution was similar for the two sexes, there being an excess of males over females in all groups, but particularly in the age groups 0–5 and 50+. Classification by type showed an excess of cases of acute over chronic leukaemia at all ages up to 76 years, the acute cases forming 61% of the total (23·7% myeloid, 23·4% lymphatic, and 13·9% unknown) compared with 33·6% for chronic cases. In the age group 0–15 years 94% of cases were acute, compared with 53% at 16–50 years and 49% among those aged over 50. Owing to the fairly large propor-

tion (13·9%) of acute cases of unknown type, the only facts emerging in this category were that 30% occurred at age 0–15 years and 46% at age over 50 years, and that acute myeloid leukaemia was uncommon in children. The authors stress the high incidence of acute leukaemia in the whole series, especially in older patients, and speculate on the possibility of a shift towards a later age of onset of the disease in general. Comparing their series with other reported studies they find general agreement concerning the chronic types, but wide fluctuations in the acute types, and ascribe this to the difficulty in typing and classifying the immature leucocytes.

In the second part of this paper the authors describe the symptoms and signs of acute leukaemia in New Zealand in patients over 50 years of age. They personally examined 25 patients and studied the case records of 72 further cases in which the information supplied unequivocally supported the diagnosis of acute leukaemia. Blast cells and myelocytes of the bone marrow were termed immature, in that they were capable of mitotic division, whereas later myelocytes and metamyelocytes were termed mature. They found that in contrast to the usual acute onset and severe symptoms and signs seen in children, acute leukaemia in elderly people was characterized by an insidious onset, with mild, non-specific symptoms and few signs, and that these were often initially attributed to other diseases such as carcinomatosis, heart failure, and pernicious or secondary anaemia. The chief symptoms were fatigue, anorexia, vomiting, infections, breathlessness, and haemorrhages. The main signs were pyrexia, pallor, purpura and haemorrhages, and palpable swellings in the spleen, liver, and lymph nodes. The duration of symptoms before diagnosis was 2 to 4 months and the mean period of survival after diagnosis was 6 weeks. Routine forms of antileukaemic therapy were uniformly unsuccessful. All the patients were anaemic at the time of diagnosis and became progressively more so, and 77% showed a lowered platelet count. The leucocyte count fluctuated markedly from patient to patient and in the same patient at different times. About 50% of the patients were sub-leukaemic at some stage, while 23% had a leucocyte count of 50,000 per c.mm. or more. The proportion of blast cells also varied markedly and erythroblasts were present in some cases. Bone-marrow smears generally showed hyperplasia of the leukaemic cells, which were usually blasts; erythroblasts and megakaryocytes were present in several cases. Necropsy revealed a variable extent of infiltration of various organs, but the bone marrow and spleen were involved in all cases. The type of infiltrating cell was as diverse as that in the marrow.

There was no correlation between the clinical and laboratory findings. The lack of response to treatment, it is suggested, may have been due to the disease being diagnosed in the terminal stages, the preceding symptoms in these patients aged over 50 having been considered too trivial to be taken seriously. The early symptoms of acute leukaemia in the elderly thus resembled those of chronic leukaemia and sharply contrasted with those of acute leukaemia in children. However, the survival time after diagnosis was much shorter than in chronic leukaemia (where the physical signs were much more prominent) and the very varied histological and haematological findings and lack of response to treatment distinguished this group from both the other groups.

M. Kendal

596. **Reticulosis with Macroglobulinaemia.** (Lymphoretikulosen mit Makroglobulinämie)
H. BRAUNSTEINER, E. OSWALD, F. PAKESCH, and E. REIMER. *Wiener Zeitschrift für innere Medizin und ihre Grenzgebiete* [*Wien. Z. inn. Med.*] **37**, 349–358, Sept., 1956. 4 figs., 23 refs.

After describing in detail 3 cases of reticulosis with macroglobulinaemia seen in 2 women aged 65 and 69 and a man of 56 at the Second University Medical Clinic, Vienna, the authors review the signs, symptoms, and associated conditions as seen in these cases and in a further 28 reported in the literature.

In 2 of the present cases there was cirrhosis of the liver and in one amyloidosis. The patients presented with symptoms of anaemia, and cryoglobulin was demonstrated as a macroglobulin with its main components on ultracentrifuging at S_f 27 and S_f 19. No Bence Jones protein was present in the urine. In all 3 cases small, sharply circumscribed, lymphoid-cell foci were found in the bone marrow, liver, kidney, pancreas, and skin.

In contrast to the findings in multiple myeloma these usually show no osteolytic growth, no pain or fractures, and the lymph nodes and spleen are rarely involved, but on the other hand haemorrhagic episodes with leucopenia and thrombocytopenia are commoner. Plasma cells, however, are numerous in the bone marrow. The proliferating cells resemble the lymphoid reticulum cells of Rohr. Electron microscopy may reveal an ergastoplasm in plasma cells, this being contained in concentrically arranged, flat, bag-like structures with a wall thickness of 40 to 60 Å., and it can be demonstrated also in other protein-secreting cells, such as those in the thyroid and prostate glands. The state of the ergastoplasm permits certain conclusions to be drawn as to the functional state of the cell. Lymphocytes have no ergastoplasm. Electron microscopy of the proliferating cells in the authors' 3 cases clearly demonstrated an ergastoplasm which, however, was not identical with that in plasma cells but resembled rather that developing in lymphoid reticulum cells during active immunization experiments with typhoid bacilli—that is, in response to antigenic stimulation.

Having thus established the potentiality of the pathological cell to secrete protein, the authors suggest that a metabolic aetiology for this condition can no longer be supported and that the disease must be classed, together with multiple myeloma, among the neoplastic reticuloses. Certain clinical and laboratory findings can be explained by the nature of the paraprotein. Thus the pseudoglobulin can be seen on electron microscopy to prevent the formation of pseudopodia and the adhesion of platelets, this accounting for the bleeding tendency in one of the cases. The dysproteinaemia of long standing may have been responsible for the cirrhosis observed in 2 of these cases.

F. Hillman

Respiratory System

597. **The Familial Occurrence of Bronchiectasis.** (Familiäres Vorkommen von Bronchiektasien)
M. KARTAGENER and K. MÜLLY. *Schweizerische Zeitschrift für Tuberkulose und Pneumonologie* [*Schweiz. Z. Tuberk.*] **13**, 221–255, 1956. 21 figs., bibliography.

In view of the increasing interest in the familial occurrence of bronchiectasis the authors, working at the University Medical Clinic, Zürich, have studied afresh the 13 cases previously reported by the first-named author in 1935, and now add 3 more personal cases, together with a review of much of the recent relevant literature. They consider familial bronchiectasis to be congenital in association with such conditions as inversion of the viscera, fibrocystic disease of the pancreas, and tuberous sclerosis. It also occurs in a group of cases without other malformations in which, the authors suggest, it is due to a hereditary disposition which has been converted into a disease by some exogenous infective factor.

In evidence of a familial and hereditary type of bronchiectasis they adduce the following observations. (1) In addition to 2 cases personally observed they cite from the literature reports of 10 sets of uniovular twins of which both members suffered from bronchiectasis. (2) To the many cases in the literature on the occurrence of bronchiectasis in siblings the authors add 2 recent cases (in addition to the senior author's original 4 pairs), and these are here reported in great detail. In the first pair, whose parents were not blood-relations and whose 5 other sibs were healthy, symptoms first occurred after pneumonia in both cases, at the age of 18 in the brother and at 13 in the sister. Widespread bilateral bronchiectasis, similar in distribution on radiological and bronchoscopic examination, was present in both; great similarity was also noted on pathological examination of the lobectomy specimens from these patients. It is pointed out that these 2 cases considered singly might well have been diagnosed as " acquired bronchiectasis " had the relationship of the patients not been known. In the case of the second pair the parents were first cousins; the father was healthy, but the mother had healed pulmonary tuberculosis. Both siblings were known to have been bronchiectatic since early childhood following recurrent attacks of bronchitis, both had malformed frontal sinuses, and both suffered from chronic maxillary sinusitis.

The authors consider bronchiectasis to be inherited recessively in cases in which no direct transmission from parents to children can be proved, or in which it occurs in children of related parents, and as a dominant character when directly transmitted from parents to children, instances of which have been reported in the literature, though none have been met by the authors. (3) The authors' observations of bronchiectasis in second cousins, while other authors have reported its occurrence in first cousins, in aunts and nephews, and in grandparents and grandchildren. (4) Many records exist of families in which several members in different generations have suffered from bronchiectasis. Statistics show that in " bronchiectatic families " the condition occurs 14 times as frequently as in the general population. In one family fully reported in this paper 5 cases occurred in 3 generations. In 3 of these cases both lower lobes were atelectatic, the atelectasis probably being secondary to bronchiectasis. In such cases the occurrence of bronchiectasis may reasonably be ascribed to a hereditary predisposition to it, especially when neither on clinical nor on anatomical grounds is there evidence of its being congenital. *E. S. Wyder*

598. **A Study of Social Factors in Chronic Bronchitis.** (Enquête sociale sur les bronchites chroniques)
P. DELORE and E. POMMATAU. *Journal de médecine de Lyon* [*J. Méd. Lyon*] **37**, 639–647, Sept. 20, 1956. 6 refs.

In this discussion, from the Institute of Social Medicine, Lyons, of the social and economic consequences of chronic bronchitis the authors state that a previous attempt to arrive at the incidence of chronic bronchitis from French mortality and morbidity statistics showed that the former were unreliable because only the immediate cause of death is certified. Thus, in 1952 in France only 2,099 deaths were certified as being due to bronchitis out of a total of 36,092 deaths from non-tuberculous respiratory diseases, but many more of these patients who died were presumably sufferers from chronic bronchitis.

In the present study morbidity figures were therefore obtained from the Social Security regional office for the area Rhône–Alpes. (Civil servants and railway and mine workers were thus excluded, since they are separately pensioned.) At December 31, 1955, a total of 25,295 persons were receiving sickness benefit from this office. The records of 684 of these cases (2·7%) in which the diagnosis was chronic bronchitis and emphysema were studied and 618 of them were classified by the authors as follows: 405 cases of chronic bronchitis and emphysema, 121 of asthma, 78 of bronchiectasis (mostly confirmed by bronchogram), and 14 of miscellaneous pulmonary infection.

Since these 618 cases were all in persons under 60 years old in whom the mean age of onset of disability was 50·5 years, since 70% were totally incapacitated at least temporarily, and since of the 405 patients with chronic bronchitis 71·6% were males, bronchitis was clearly causing an important loss of working capacity. The authors then present figures of the various nationalities (36·6% of the invalids receiving disability pensions were born outside France) and occupations, from which certain conclusions are drawn regarding the importance of changes of climate and of temperature at work or dust exposure in the aetiology of bronchitis. [Since, however, no figures for the distribution of these

nationalities or occupations in the general population are given, these conclusions cannot be regarded as valid.]

The authors compare their findings with those of a number of different workers in Great Britain. They conclude by emphasizing the great importance of bronchitis as a cause of invalidism and calculate [without giving any details] that 10% of all disability pensions disbursed in France are paid on account of chronic bronchitis. *C. M. Fletcher*

599. **Long-term Chemotherapy in Chronic Bronchitis**
J. R. MAY and N. C. OSWALD. *Lancet* [*Lancet*] **2**, 814–818, Oct. 20, 1956. 12 refs.

A series of 37 patients with chronic bronchitis at the Brompton Hospital, London, were given a maintenance dose of tetracycline or oxytetracycline during the 6 winter months of 1955–56, the dose being the lowest that would maintain the sputum free from pus; if side-effects occurred the dose was reduced. Patients were seen monthly, when the volume and purulence of the sputum, respiratory symptoms, and side-effects were recorded. During the previous winter 14 of the patients had daily recorded their own observations on sputum, and these patients were regarded as a "controlled" group, since their observations were a useful objective index of the behaviour of chronic bronchitics under "normal" conditions. Of these 14 patients, 4 failed to tolerate an adequate dose of either drug because of diarrhoea; in one the bronchitic condition was unchanged, but in 9 the daily volume of sputum was reduced, the amount of pus was diminished, and acute exacerbations were less frequent. There was no consistent effect on dyspnoea. Of the 23 patients for whom there was no control period, 8 had to stop treatment or reduce the dose because of diarrhoea, 10 appeared to be considerably improved, and 5 showed no clinical benefit. In patients who improved the maintenance dosage varied from 0·25 to 1·5 g. daily. At the end of the treatment tetracycline-resistant staphylococci were present in the sputum or anterior nares of one-quarter of the patients.

It is concluded that maintenance treatment with tetracycline or oxytetracycline will produce improvement, often striking, in about half the patients with bronchitis who have a persistent purulent sputum, but that the development of resistant organisms, especially staphylococci, is a danger which needs watching.
C. M. Fletcher

600. **Topical and Systemic Chemotherapy of Suppurative Lung Disease**
E. J. GRACE. *International Record of Medicine* [*Int. Rec. Med.*] **169**, 631–635, Oct., 1956. 12 refs.

The author is an advocate of combined chemotherapy in the treatment of pulmonary conditions since with this form of treatment smaller amounts of the drugs are required and the emergence of resistant bacterial strains is prevented or delayed.

In this paper he summarizes the results of such treatment as observed in 34 patients in private practice, of whom 23 suffered from pulmonary tuberculosis, 9 from bronchiectasis, and 2 from non-tuberculous pulmonary abscess. Treatment consisted in the administration of the complex "streptohydrazid" (streptomycyclidene *iso*nicotinyl hydrazine sulphate) intramuscularly, PAS and isoniazid orally, and these same antituberculous agents given topically, that is, by deep inhalation of a detergent mist containing the drugs.

The patients with pulmonary tuberculosis were followed up for from one to 9 years, 16 of them being under observation for at least 3 years. More than six consecutive negative cultures of the sputum were obtained in 14 of these cases, three consecutive negative cultures so far in one, but in the last case the sputum remained positive during the 3 years of treatment; nevertheless the infecting organism in this case remained sensitive to both streptomycin and isoniazid. Of the 7 patients observed for less than 3 years, at least six consecutive negative sputum cultures have been obtained in 2, in 3 cases the cultures have remained positive, while the remaining 2 patients, in whom the disease was far advanced, have died. All 9 patients with bronchiectasis and the 2 with pulmonary abscess responded well to combined penicillin and streptomycin treatment. No adverse side-effects and no development of drug resistance were encountered in any of the 34 cases.
K. Zinnemann

601. **The Viscous Resistance of Lung Tissue in Patients with Pulmonary Disease**
R. MARSHALL and A. B. DUBOIS. *Clinical Science* [*Clin. Sci.*] **15**, 473–483, Nov., 1956. 18 figs.

602. **Fatal Pulmonary Insufficiency Due to Radiation Effect upon the Lung**
D. J. STONE, M. J. SCHWARTZ, and R. A. GREEN. *American Journal of Medicine* [*Amer. J. Med.*] **21**, 211–226, Aug., 1956. 8 figs., 23 refs.

Fibrosis of the lung as a result of *x*-irradiation is a well-established clinical entity. In this paper from the Veterans Administration Hospital, Bronx, New York, 5 cases are reported in which, following radiotherapy for intrathoracic malignant disease (carcinoma of the bronchus in 2 and Hodgkin's disease, seminoma metastases, and testicular embryonic carcinoma metastases each in one), death occurred in severe pulmonary insufficiency and at necropsy gross pulmonary fibrosis was found in areas largely corresponding to those irradiated. From the results of pulmonary function studies the authors consider that an impaired diffusion across the alveolar–capillary membrane was the most important factor in each case. The development of radiation pneumonitis and fibrosis appeared to be related to the amount and the duration of *x*-irradiation, in that intense irradiation over a short period of time was more likely to produce fibrosis than the same amount of irradiation over a longer period.

Steroid therapy failed to alter the course of the disease [nor was administration of these hormones found to be of any value prophylactically by Chu *et al.*, *Amer. J. Roentgenol.*, 1956, **75**, 530.] *J. Warwick Buckler*

Otorhinolaryngology

603. **Benjamin Franklin—" The Rhinologist "**
H. F. FLIPPIN. *A.M.A. Archives of Otolaryngology* [*A.M.A. Arch. Otolaryng.*] **63**, 541–551, June, 1956. 9 refs.

[The title of this paper is misleading, a brief reference to Benjamin Franklin serving only as the introduction to a comprehensive and careful review of the present state of antimicrobial therapy in otorhinolaryngology. It should be studied in full.]

F. W. Watkyn-Thomas

604. **Radiology in Late Congenital Syphilitic Nerve Deafness**
R. S. MORTON. *British Journal of Venereal Diseases* [*Brit. J. vener. Dis.*] **32**, 162–164, Sept., 1956. 2 figs., 8 refs.

Forty congenital syphilitics, including 6 with late congenital syphilitic nerve deafness, have had their petrous temporals examined radiologically. The results are substantially negative. These negative findings seem to support the suggestion that late congenital syphilitic nerve deafness is a hypersensitivity phenomenon. Further research is indicated.—[Author's summary.]

605. **Mobilization of the Stapes for Otosclerosis. A New and Safe Technique**
M. C. MYERSON. *A.M.A. Archives of Otolaryngology* [*A.M.A. Arch. Otolaryng.*] **64**, 85–90, Aug., 1956. 7 figs., 9 refs.

The author describes a " new and safe technique " for mobilization of the stapes in which a " forked instrument " is applied to the incudo-stapedial junction and held in place. A rod inserted in the chuck of a dental drill is then laid against the shaft of the fork and set in motion, causing the fork to vibrate at three different speeds corresponding to 1,500, 5,000, and 9,000 revolutions per minute of the rotating rod. If this does not free the footpiece, direct mobilization by the method of Rosen is tried. If this too fails the fenestration operation is advised. From experiments on the cadaver the author concludes that the vibrations set up by the revolving rod at 9,000 r.p.m. will mobilize any stapes that can be dislodged without permanent damage.

F. W. Watkyn-Thomas

606. **Anatomical Factors in Stapes-mobilization Operations**
M. BASEK and E. P. FOWLER. *A.M.A. Archives of Otolaryngology* [*A.M.A. Arch. Otolaryng.*] **63**, 589–597, June, 1956. 14 figs., 14 refs.

In a study of the anatomical factors concerned in the mobilization of the stapes in otosclerosis the mechanism of movement of the normal and fixed stapes was observed at the College of Physicians and Surgeons, New York, in over 100 temporal bones from fresh cadavers; the methods of investigation, which included slow-motion cinematography, are fully described. As the usual site of fixation is anterior—that is, of the footpiece to the edge of the fenestra—the logical procedure would seem to be to fracture the footpiece behind the area of fixation and to divide the anterior crus, thus leaving the posterior part of the footpiece still attached to the posterior crus, and restoring mobility to the ossicular chain. As there is good evidence that a fracture of the footpiece heals by fibrous union and not by bone, it is reasonable to hope that the mobility and the consequent gain in hearing so restored might be permanent.

F. W. Watkyn-Thomas

607. **Neomycin–Hydrocortisone Acetate in Otitis Infections**
J. T. LEES. *Journal of Laryngology and Otology* [*J. Laryng.*] **70**, 568–573, Oct., 1956. 11 refs.

The ideal antibiotic for local application in otitic infections is one which is not generally given systemically. Neomycin, a wide-spectrum antibiotic, has been used topically without giving rise to sensitization, while hydrocortisone ointment is known to be effective locally in the relief of itching and inflammation. At the Glasgow Royal Infirmary both an ointment and an aqueous solution containing 1·5% hydrocortisone acetate and 0·5% neomycin sulphate have been tried in the treatment of otitic infections in 63 patients. Acute diffuse external otitis cleared up well in each of the 19 cases. The results in 17 cases (22 ears) of chronic diffuse external otitis were classified as excellent in 10 ears, good in 6, and fair in 6. The response to treatment of infected radical mastoid cavities was " surprisingly good ", there being healing in 8 of the 19 cases. Dry ears were obtained in 8 cases of otitis media in which the perforation was central. In all cases swabs were taken from the ears before treatment and cultured, the commonest organism found being *Staphylococcus aureus*. *H. D. Brown Kelly*

608. **Deafness and Vertigo from Head Injury**
H. F. SCHUKNECHT and R. C. DAVISON. *A.M.A. Archives of Otolaryngology* [*A.M.A. Arch. Otolaryng.*] **63**, 513–528, May, 1956. 8 figs., 47 refs.

The auditory and vestibular symptoms which may follow head injury can be classified according to the kind of labyrinthine damage: (1) longitudinal fracture of the temporal bone; (2) transverse fracture; and (3) labyrinth concussion.

Longitudinal fracture, which constitutes 80% of all temporal bone fractures, presents as a linear fracture through the floor of the middle fossa, parallel and close to the anterior margin of the petrous pyramid, from the Gasserian ganglion to the middle ear and mastoid, traversing the tympanic ring and membrane, and sometimes causing damage to the bony meatus and " step-

like " deformity of the canal. In some cases there may be dislocation of the incudo-stapedial joint, in some, escape of cerebrospinal fluid, while facial paresis, usually temporary, occurs in 25% of cases. The deafness is usually of middle-ear type, due to interference with the conduction mechanism either by direct injury to the ossicles or by blockage with blood, but is usually transient and passes off in 6 weeks or so. But in some cases there is also concussion injury to the cochlea, and in this event complete recovery of hearing is rare, although some improvement is the rule. Transient vertiginous attacks, lasting only for a few seconds and usually brought on by head movements, are frequently observed and sometimes persist for months after the injury. They may be due to damage to the pathways, but are probably more often the result of damage to the vestibular labyrinth. In radiographs the line of fracture can usually be seen as a streak in the squamous portion, and the mastoid cells are clouded by retained blood or cerebrospinal fluid.

Transverse fractures, which are most often caused by blows on the occiput, traverse the vestibule. In 50% of cases there is facial paralysis, sometimes permanent. Bleeding from the meatus is rare, as the tympanic membrane is seldom torn. Haemotympanum is usual, and blood and cerebrospinal fluid escape down the eustachian tube. There is generally complete and permanent loss of hearing and of vestibular function. The vertigo is typical of destruction of the labyrinth, usually subsides in 2 or 3 weeks, but some unsteadiness may persist for months. Occasionally the fracture may be limited to the labyrinthine capsule. Isolated fractures of the internal meatus or the cochlea have been found in post-mortem specimens. In 60% of cases the fracture is visible on radiographs.

Finally, the authors discuss labyrinthine concussion, defined as " perceptive deafness and vertigo resulting from a blow on the head without fracture of the bony labyrinth capsule ". It is most common with a longitudinal fracture on the same side, next most common in the ear opposite a temporal fracture, and is least commonly found in a head injury with no evidence of fracture. Usually a blow severe enough to cause concussion of the labyrinth also causes loss of consciousness, but a moderate blow, especially on the occiput, can cause permanent deafness. Hearing loss is greatest for high frequencies, with the peak at 4,000 c.p.s., and the vertigo is usually of the postural type. Animal experiments have shown that the deafness is due to injury of the organ of Corti, and is identical with that caused by a shock pulse in air, as in explosion blast. Probably the blow to the head creates a bone-conducted pressure or sound wave which injures the cochlea. Histological examination of experimental animals showed that the greatest damage was to the outer hair cells in the upper basal turn—the region serving the 4,000-c.p.s. frequencies. Thus a blow on the head, like a blast of air, violently displaces the basilar membrane, so that injury is caused to the organ of Corti. Positional nystagmus, which may occur without deafness, sometimes after a mild jar, is probably due to injury by linear acceleration to the utricle or saccule. *F. W. Watkyn-Thomas*

609. **The Diagnosis and Treatment of Ménière's Disease** T. E. WALSH. *A.M.A. Archives of Otolaryngology* [*A.M.A. Arch. Otolaryng.*] **64**, 118–128, Aug., 1956. 2 figs., 18 refs.

The author presents a review of 127 recent cases of Ménière's disease. Pure-tone audiograms followed the accepted pattern, that is, first loss of low tones, then a flattened curve, and later increasing loss of high tones. Speech audiography showed much greater loss of discrimination than the pure-tone audiogram suggested. Recruitment was always present in the affected ear, and diplacusis was usual, though sometimes for only one frequency. Caloric tests by the method of Fitzgerald and Halpike gave in early stages equal response of canal paresis on the affected side, but later there was diminished response from both sides, or in a few cases no response from either side. Spontaneous nystagmus was seen only during an attack. Ménière's disease is more common in men than in women (55% to 45%), occurs most frequently after the age of 40, and most commonly affects one ear only (83·5% of cases).

The object of treatment is to overcome a spastic, atonic state of the cochlear vessels and relieve vasomotor labyrinthine ischaemia. As possible aetiological factors include allergies, endocrine dysfunction, and psychosomatic factors there is no one specific medical therapy. Vasodilator drugs and nicotinic acid may often relieve vertiginous attacks, but the present author has never found that they produced any improvement in hearing. Since acetazolamide has been very successful in the treatment of glaucoma, this author has tried it in the hope that secretion of endolymph might be inhibited, as is the secretion of the ciliary body. Here again in 2 cases there was improvement of the vertigo but no improvement in hearing. In his use of histamine the author starts with 0·1 ml. of the dilution that gives the least positive reaction, and increases the dose by 0·1 ml. every third day until relief is obtained. In some cases vertigo, tinnitus, and hearing have all been greatly improved, but in 2 cases in which the optimum dose was exceeded all the symptoms recurred. He is not impressed by the results of a salt-free diet, but has obtained good results with cyanocobalamin (vitamin B_{12}). If these medical measures produce no relief, then in cases of long standing and where only one ear is affected destruction of the labyrinth may be performed. Relief by section of the eighth nerve " is only mentioned to be deprecated ". Differential section is justified only when there is bilateral hearing loss and one ear can definitely be incriminated for the vertiginous attacks. Diathermy coagulation has not proved very successful. Cawthorne's method of labyrinthotomy and removal of the membranous labyrinth with fine forceps is mentioned, but the present author believes that complete destruction of the vestibular labyrinth is essential. His practice is to open the vestibule, together with the ends of the superior and horizontal canals, remove all neural elements of the vestibule, and pack the opening with bone chips saved from exenteration of the mastoid cells. Of 37 patients operated on, 35 were completely relieved of their symptoms, while 2 developed hydrops in the other ear.

F. W. Watkyn-Thomas

Urogenital System

610. **The Vascular Pattern of the Renal Glomerulus as Revealed by Plastic Reconstruction from Serial Sections**
C. C. BOYER. *Anatomical Record* [*Anat. Rec.*] **125**, 433–441, July [received Oct.], 1956. 6 figs., 15 refs.

In 1686 Malpighi, in his *De Renibus*, described branching and anastomoses in the vessels of the renal glomeruli, but this concept has been ignored or contradicted in most subsequent descriptions. The present author, at the University of Alabama, has made plastic models based on serial sections of glomeruli injected with indian ink, from which he has shown that the glomerulus is not a series of capillary loops connecting the afferent and efferent arterioles, but is a true network similar to capillary networks elsewhere in the body. *T. B. Begg*

611. **Changes in the Renal Circulation during the Course of Chronic Glomerulonephritis.** (Le remaniement de la circulation rénale au cours de la glomérulonéphrite chronique)
N. GOORMAGHTIGH. *Revue belge de pathologie et de médecine expérimentale* [*Rev. belge Path.*] **25**, 182–189, July, 1956. 4 figs., 9 refs.

In an investigation carried out at the University of Ghent an attempt was made, by means of the study of serial sections of renal tissue, to reconstruct the pathological changes in the kidneys in chronic glomerulonephritis, particular attention being paid to the vascular changes. It was found that juxta-medullary glomeruli became canalized, this being followed by formation of vasa recta. Vascular connexions between atrophic glomeruli were shown to develop, whereas the afferent arterioles supplying the regressive glomeruli showed progressive obstruction of their lumina, quite unlike the process in arteriosclerosis. The arterioles became stumps, and their muscular cells began to show a granular content. The author suggests that these cells function as an endocrine organ producing a vasopressor substance. As the disease progresses and the vascular bed contracts these cells are continuously formed and thus may contribute to the maintenance of general arterial hypertension. *G. W. Csonka*

612. **Urinary Excretion of Amino-acids and Sugar in the Nephrotic Syndrome. A Chromatographic Study.** [In English]
L. I. WOOLF and H. MCC. GILES. *Acta paediatrica* [*Acta paediat. (Uppsala)*] **45**, 489–500, Sept., 1956. 4 figs., 19 refs.

The examination, by means of paper chromatography, of the urine of 29 children with the nephrotic syndrome at the Hospital for Sick Children, Great Ormond Street, and St. Mary's Hospital, London, showed that aminoaciduria was present in 25 cases at some phase of the illness and glycosuria in 16. Most of the abnormal chromatograms could be grouped in one or other of two patterns. In the first, the amino-acid pattern approximated to that of normal blood, but with proline, leucine, valine, and alanine predominating; in the second type there was increased excretion of ethanolamine, β-amino-*iso*butyric acid, taurine, tyrosine, leucine, and valine, resembling the picture found in hepatic dysfunction associated with deranged amino-acid intermediary metabolism. Some of the specimens of urine showed a mixed pattern.

It is believed that these findings were due to a true amino-aciduria. A pattern similar to that of the first type above is known to occur in conditions in which the renal tubules do not absorb amino-acids efficiently. In the present series this pattern was found mainly in cases suspected on other grounds of having irreversible renal damage, this view being supported by the presence of concomitant glycosuria in these cases. Interpretation of the second type of pattern is more difficult. The patients with this type showed a greater tendency to recover, revealed no evidence of renal failure, fewer of them had accompanying glycosuria, and the blood amino-acid level was not raised. It is suggested that two causes may be responsible for the second type of pattern: (1) a renal tubular leak resulting in the appearance of leucine, valine, and perhaps tyrosine in the urine, and (2) a metabolic disturbance causing the appearance of ethanolamine, taurine, and β-amino-*iso*butyric acid. *G. W. Csonka*

613. **Nitrofurantoin in Chronic Urinary Infection Associated with Renal Calculi**
M. G. MCGEOWN. *British Medical Journal* [*Brit. med. J.*] **2**, 274–276, Aug. 4, 1956. 9 refs.

The results of the use of nitrofurantoin, (N-(5-nitro-2-furfurylidene)-1-aminohydrantoin; "furadantin") in the treatment of 21 cases of refractory urinary infection associated with renal calculi or persisting after their removal are reported from Queen's University, Belfast. A large dosage was used, 10 mg. per kg. body weight per 24 hours being given for 14 days to 14 patients; the remaining 7 could not tolerate the full course owing to nausea or vomiting or both. The age of the youngest was 2½ years. In 10 cases the urine became sterile. It remained so for 3 months in 6 cases and for 5 months in one case. To this extent nitrofurantoin was effective against both Gram-positive and Gram-negative organisms and was "particularly useful" against enterococci, staphylococci, and *Proteus*. *W. Skyrme Rees*

614. **The Reduction of Postnephrectomy Hypertension by Renal Homotransplant**
E. E. MUIRHEAD, J. A. STIRMAN, W. LESCH, and F. JONES. *Surgery, Gynecology and Obstetrics* [*Surg. Gynec. Obstet.*] **103**, 673–686, Dec., 1956. 8 figs., 29 refs.

Endocrinology

615. **Hyperparathyroidism and Steatorrhoea**
D. R. Davies, C. E. Dent, and A. Willcox. *British Medical Journal* [*Brit. med. J.*] **2**, 1133–1137, Nov. 17, 1956. 11 figs., 10 refs.

Two cases of steatorrhoea seen respectively at the Middlesex Hospital and University College Hospital, London, are described in which there was evidence of hyperparathyroidism as well as of osteomalacia. The first patient was a woman aged 37 years who had a 10-years' history of diarrhoea and had suffered for 16 months from pain in the bones. The second was a woman aged 41 years whose condition suggested life-long steatorrhoea, although in fact she was constipated, and who had complained of bone pains for 11 years. In both cases radiography showed a combination of three conditions: (1) osteomalacia, of acute onset in Case 1, as shown by the presence of Looser's zones in the pelvis but no deformities, and of long duration in Case 2, as shown by the trefoil pelvis; (2) hyperparathyroidism, as suggested by the presence of subperiosteal erosions in the phalanges of the fingers in both cases and the "fuzzy" appearance of the skull and other bones in Case 2; (3) osteosclerosis, as revealed by the increased density of the upper and lower regions of the vertebrae (the "rugger jersey" sign). In Case 1 the serum calcium level varied between 9 and 10 mg. per 100 ml. and the serum phosphorus level was below 2 mg. per 100 ml.; the alkaline-phosphatase figure was 75 King–Armstrong units. In the second case the serum calcium level was between 11 and 12 mg. per 100 ml., the phosphorus level 2 mg. per 100 ml., and the alkaline-phosphatase content 69 units.

In the first patient, who became pregnant and was successfully delivered by Caesarean section, recalcification of the bones and loss of symptoms followed the pregnancy, during which calciferol was given in doses of up to 250,000 units daily. In the second patient calcium balance studies showed a high faecal calcium content, which was reduced only slightly by the administration of dihydrotachysterol, as would be expected in steatorrhoea; there was no improvement in the radiological appearances of hyperparathyroidism, although the treatment produced partial relief of symptoms. Exploration of the neck revealed a chief-cell adenoma of one parathyroid gland and the presence of two other normal parathyroid glands, but a fourth gland could not then be identified. After removal of the adenoma there was a slow fall in the serum calcium level, the pains disappeared, and the subperiosteal erosions improved, but pale, loose stools typical of frank steatorrhoea appeared; although the serum calcium level eventually returned to normal the serum phosphorus level remained low. Later, the osteomalacia and hyperparathyroidism relapsed (with a return to constipation) and re-exploration of the neck revealed a second adenoma in the fourth parathyroid gland, removal of which was followed by severe tetany but eventually led to permanent relief of symptoms and a trend in the serum calcium levels and radiological appearances towards normal, although diarrhoea again appeared.

These two cases confirm that hyperparathyroidism (and the radiological appearances thought to be specific for this condition) may arise, in addition to osteomalacia, in steatorrhoea as well as in renal osteodystrophy. It appears that the condition is initially one of parathyroid hyperplasia, which can be reversed by the administration of calciferol, as in Case 1, but in other cases one or more adenomata may later develop, which require surgical removal, as in Case 2.

Robert de Mowbray

THYROID GLAND

616. **Inhibition of Thyroidal Radioiodine Uptake following Intravenous Administration of Thyroxine to Normal and to Hypophysectomized Adult Subjects**
N. E. Sharrer and S. P. Asper. *Journal of Clinical Endocrinology and Metabolism* [*J. clin. Endocr.*] **16**, 1311–1325, Oct., 1956. 1 fig., 20 refs.

The authors, from the Johns Hopkins University, report the results of an investigation into the effect of thyroxine on thyroid activity. The investigation was carried out in two parts: (1) observation of the acute effect of intravenously administered thyroxine on thyroid activity; and (2) study of its long-term effects. The clinical material included 33 euthyroid subjects and 2 recently hypophysectomized patients.

In the first part of the investigation 10 subjects were given DL-thyroxine intravenously in doses ranging from 0·75 to 5 mg. 2 hours after an oral dose of radioactive iodine (^{131}I). In 4 of the subjects uptake of ^{131}I by the thyroid ceased at 30 to 90 minutes after thyroxine administration, and was not resumed until after one to 2½ hours had elapsed. This suppressive effect was only slight in 3 subjects and absent in a further 3. To test whether this effect was due to the iodine content of the thyroxine, 3 subjects were given 3·4 mg. of potassium iodide, the iodine equivalent of 4 mg. of thyroxine. This produced complete cessation of uptake of ^{131}I by the thyroid gland in 2 subjects.

In the second phase of the study ^{131}I uptake was measured in 22 subjects at periods of 4 hours to 40 days after the intravenous injection of 3 mg. of DL- or L-thyroxine. The inhibitory effect of exogenous thyroxine on thyroidal ^{131}I uptake was evident on the first day, moderate within 4 days, maximum between the 7th and 9th days, and detectable for 14 days. This depression was thought not to have been related to multiple ^{131}I tracer doses. Uptake of ^{131}I by the thyroid was found to be reduced by hypophysectomy, but no further reduction was noted following administration of exogenous

thyroxine. Uptake of ^{131}I, reduced by hypophysectomy, could be returned to normal by administration of thyrotrophic hormone, and this restorative action of thyrotrophin was still fully effective after exogenous thyroxine had been given. The pattern of reduced thyroidal uptake of ^{131}I after hypophysectomy was very like that following intravenous injection of thyroxine both in type and in time.

It is concluded that the inhibitory action of exogenous thyroxine is not on the thyroid but on the output of thyrotrophin. The 7-day time lag before the maximum effect appears is thought to be due to free circulating thyrotrophin. The transient depression of thyroid uptake of ^{131}I occurring within 2 hours of thyroxine administration is considered to be a free iodide effect.

J. N. Harris-Jones

617. **The Dilemma of the Nontoxic Nodular Goiter**
W. R. SCHILLHAMMER and R. I. CRONE. *Annals of Internal Medicine* [*Ann. intern. Med.*] **45**, 480–489, Sept., 1956. 32 refs.

In this paper from the Letterman Army Hospital, San Francisco, the authors discuss the possible relationship between carcinoma of the thyroid gland and nontoxic nodular goitre. In a series of 165 patients undergoing surgery following the confirmed diagnosis of nontoxic nodular goitre or thyroid carcinoma there were 40 cases of asymptomatic benign goitre, 4 of asymptomatic carcinoma, 98 of symptomatic benign goitre, and 23 of symptomatic carcinoma. The over-all incidence of carcinoma in patients with symptoms was 19% and in those without symptoms 9·1%. All the cases of carcinoma occurred in association with nodular goitre, and none with diffuse goitre. The commonest and sometimes the only sign in both groups was a painless lump in the neck. Pressure symptoms were of little value in differentiating cancer from benign lesions, although they tended to occur somewhat more frequently in the benign cases. The average age of the entire group was 39·2 years, that of patients with benign lesions 41·1 years, and of those with carcinoma 33·2 years. The ratio of females to males with goitre was 4:1, while in the patients with carcinoma it was 3:1. The physician was accurate in his diagnosis of the type of node, as compared with the findings of the pathologist, in only 48% of cases. Twelve general types of operation were performed on 138 cases of benign nodular goitre which would seem to indicate, as the authors point out, some measure of doubt concerning the surgical procedure of choice.

The frequency of carcinoma in nodular goitre has been reported to be alarmingly high—up to 17%. Postmortem studies reported in the literature show the incidence of nodular goitre to vary from 4·5 to 88% depending upon the geographical origin of the series, while the frequency of thyroid cancer has been reported to be about 0·1% of all cases, and about 0·56% of all cases of cancer. Sokol has calculated on the basis of a hypothetical population that the true incidence of cancer in non-toxic goitre should be only about 0·2%. It is suggested that this discrepancy is largely attributable to the manner in which patients are selected. Some selection is practised first by the patient himself, who rarely seeks medical advice unless the gland is enlarged or there is a change in its activity, and again by the physician, who quickly refers readily identifiable and suspected glands to the surgeon, who further selects the cases according to his opinions and criteria for operation. The incidence of carcinoma in this series (16·4%) is representative of a highly selected group, as 8 of the cases of cancer were referred to the hospital from elsewhere and, further, this hospital receives complicated cases from a wide area. All the patients were active or retired military personnel or their dependents.

It is pointed out that statistics in favour of nodular goitre being a pre-cancerous lesion are prejudiced by the fact that patients with symptoms are more likely to seek advice and these are also the most likely to have cancer; probably the vast majority of nodular goitres, being asymptomatic, are never seen. Though the solitary nodule is generally accepted as a potentially precancerous lesion, the failure of the physician to diagnose the exact degree of nodularity of a given gland, as has been apparent in this and other series, detracts from the value of this finding as a criterion of malignancy. Tests with radioactive iodine may prove to be of value in the differentiation of benign and malignant nodules. It is concluded that the whole problem warrants further long-term study and that until these results are available operation should be recommended in most cases of non-toxic nodular goitre.

L. G. Fallows

618. **Subacute Thyroiditis. Report of Three Cases Treated with Cortisone**
A. MOLDOVER. *A.M.A. Archives of Internal Medicine* [*A.M.A. Arch. intern. Med.*] **98**, 322–327, Sept., 1956. 28 refs.

ADRENAL GLANDS

619. **Evaluation of Adrenal Cortical Function by Stimulation with Corticotropin (ACTH)**
N. H. ENGBRING, R. B. TRUITT, and W. W. ENGSTROM. *A.M.A. Archives of Internal Medicine* [*A.M.A. Arch. intern. Med.*] **98**, 257–265, Sept., 1956. 3 figs., 8 refs.

A test for adrenal cortical insufficiency, by observing the capacity of the adrenal cortex to respond to ACTH stimulation, was investigated at Marquette University School of Medicine, Milwaukee. In each case urine was collected for two 24-hour periods to determine control values for 17-ketosteroids and corticosteroids. During the 3 subsequent days corticotrophin was administered. Urine collections were continued during this period and on the 2 following days, and steroid values compared with the control values. The excretion of 17-ketosteroids was determined by the Callow–Zimmerman method (*Endocrinology*, 1943, **33**, 229); that of corticosteroids by the sodium bismuthate method of Norymberski (*Biochem. J.*, 1953, **55**, 371). Corticotrophin was administered by two methods: (1) 35 patients were given 20 or 25 *U.S.P.* units of corticotrophin in a 5% dextrose solution intravenously over a

period of 5 to 6 hours daily for 3 days; (2) 22 patients were given 40 commercial units of an intramuscular repository corticotrophin preparation every 12 hours for 3 days. All these patients suffered from a variety of acute and chronic diseases. For comparison similar tests were carried out on 4 patients with Addison's disease and 6 patients with anterior pituitary insufficiency.

The maximum increase in steroid excretion usually occurred on the 3rd day of corticotrophin administration; exceptionally it occurred either before or after. With control values of steroid excretion greater than 2 mg. in 24 hours, increments greater than 100% in either 17-ketosteroid or corticosteroid excretion were considered an adequate response; when control levels were less than 2 mg., only increments over 200% were considered significant. By these criteria only 3 of the 57 patients failed to respond adequately. If 17-ketosteroid determinations alone are considered, the number of failures is quite high; with corticosteroid excretion alone it is less; when both are considered, only the small percentage of patients with intact adrenals failed to respond. Intramuscular injection of corticotrophin produced more pronounced and prolonged stimulation of the adrenals than did intravenous administration.

The response in 6 patients with anterior pituitary insufficiency was similar to that of the control group. In the 4 patients with Addison's disease the urinary steroid values did not significantly change when corticotrophin was administered. *Kenneth Stone*

620. **Hypersecretion of Aldosterone in Cushing's Syndrome and Disease.** (L'hypersécrétion d'aldostérone dans le syndrome et la maladie de Cushing)
J. P. DORET. *Semaine des hôpitaux de Paris* [*Sem. Hôp. Paris*] **32**, 2921–2928, Sept. 30, 1956. 1 fig., bibliography.

The author describes 2 cases of Cushing's syndrome seen at the Cantonal Hospital, Geneva, and cites a third similar case from the literature, in all of which there were metabolic abnormalities consisting mainly in the retention of sodium and water, clinically manifested by oedema, and a low serum potassium level accompanied by alkalosis. These changes were thought to be due to increased secretion of aldosterone and the urinary excretion of steroids was therefore investigated.

The first patient had a large chromophobe adenoma of the pituitary gland and an increased excretion of corticosteroids was found. In the case quoted from the literature there was a basophil adenoma of the pituitary, with diabetes mellitus, retention of sodium, and hypokalaemia; experiments on rats with this patient's urine showed that it contained an increased amount of a "sodium-retaining factor". The third patient had a mixed adenocarcinoma of the pituitary, and an increased excretion of 17-ketosteroids, corticosteroids, and aldosterone in 24-hour specimens of urine was observed. It is considered that the electrolyte abnormalities in these cases were due to hypersecretion of mineralocorticoids, and in particular aldosterone (in one case the excretion of aldosterone reached 36·4 μg. in 24 hours). The great theoretical interest of these cases lies in the finding of increased secretion of aldosterone in patients with a primary pituitary lesion, which in 2 cases was confirmed at necropsy. The author suggests that the increased secretion of aldosterone may be effected by a rise in the production of adrenocorticotrophic hormone. *I. McLean Baird*

DIABETES MELLITUS

621. **Studies on the Kinetics of Glucose Utilization**
C. J. HLAD, H. ELRICK, and T. A. WITTEN. *Journal of Clinical Investigation* [*J. clin. Invest.*] **35**, 1139–1149, Oct., 1956. 4 figs., 20 refs.

Some theoretical aspects of the kinetics of glucose utilization and a method for computation of glucose "space" are described. One hundred five studies were performed in 81 normal men using either a single injection or continuous infusion technique. Data are presented which support the derived equations. No evidence was obtained to indicate that excess insulin is released in response to the intravenous administration of glucose. The volume of distribution of glucose is discussed and evidence is presented which suggests an expansion of this "space" with increased blood sugar levels.—[Authors' summary.]

622. **Lente Insulin. Four Years' Experience**
A. G. SPENCER and M. E. MORGANS. *Lancet* [*Lancet*] **2**, 1013–1017, Nov. 17, 1956. 4 figs., 16 refs.

The authors, from University College Hospital, London, report their experience in treating 200 diabetic patients with a single daily injection of lente insulin (I.Z.S.), each patient receiving treatment for 6 months or longer during the period 1952–6. Of the 200 patients, 141 had previously been treated with other insulin preparations, 38 had been controlled by diet alone, and 21 were new, untreated diabetics requiring insulin. Of those previously treated with other insulin preparations, 102 had been on protamine zinc insulin (P.Z.I.) alone or a mixture of soluble insulin (S.I.) and P.Z.I.; 28 had been on globin insulin in single or twice-daily injections, and 11 on multiple daily injections of S.I. Treatment with I.Z.S. was given to 177 patients in the out-patient department, only 23 being admitted to hospital for this purpose. The distribution of carbohydrate and calories throughout the day was adjusted to provide substantial snacks at 11 a.m. and 10 p.m. The initial dose of I.Z.S. was usually equal to the previous total daily dose of other preparations plus 10%. Control was assessed by twice-daily urinary sugar estimations, serial blood sugar estimations, and weekly weighing of patients.

Of the patients previously treated with other insulins, 51 (36%) were better controlled with I.Z.S., 66 (47%) were as well controlled, and 24 (17%) less well controlled. In 56% of cases the amount of I.Z.S. required was within $\pm$10% of their previous total daily dose, 28% of patients needed a considerably increased dose of I.Z.S., ranging from 10 to 50% more than their previous dose, and in 8% of cases the amount of I.Z.S. required was 50 to 100% more than previously. In only 8% of cases was

the amount of I.Z.S. required less than that of the insulin formerly given. Hypoglycaemic reactions were experienced by 104 (52%) of the patients while on I.Z.S., while the remaining 96 (48%) had no reactions either on this or on their former insulin. The reactions were generally mild and the onset was recognized by the patient, but in 26 cases (16%) reactions were more frequent or more severe than with the previous insulin. Only 4 of the 200 patients were admitted to hospital with ketosis over the 4-year period. Local insulin reactions were uncommon. One patient who had never previously had insulin developed fat atrophy, but 7 others who had persistent local reactions with their previous insulin had no such reactions with I.Z.S. Treatment with I.Z.S. was abandoned in 9 cases (4%). In 4 cases this was at the request of the patient, who claimed to feel better on the old regimen, in 3 because of recurrent hypoglycaemic reactions, and in the remaining 2 cases because of intercurrent infection.

The authors claim that their observations show that in most patients diabetes can be satisfactorily controlled with a single daily injection of I.Z.S., and that many are improved by transfer from other insulins. They state that the transfer to I.Z.S. can be achieved satisfactorily under out-patient supervision provided the patient is cooperative and the total daily dose required does not exceed 80 units. There is, however, no outstanding advantage in changing a patient to I.Z.S. if he is well controlled and content on his present insulin.

John Lister

623. **Insulin Zinc Suspension. Four Years' Experience**
M. JERSILD. *Lancet* [*Lancet*] **2**, 1009–1013, Nov. 17, 1956. 12 figs., 6 refs.

The author reports his experience in the treatment of 1,000 diabetic patients (512 males and 488 females) with insulin zinc suspension (lente insulin) at Hvidøre Hospital, Copenhagen. Of these, 90% were admitted to hospital for control with the new preparations, the remaining 10% being treated as out-patients. In 10% of the patients the diabetes was of less than one year's duration, and in 50% it had been present for more than 10 years; 74% were controlled on lente insulin alone, 12% on lente insulin plus amorphous insulin zinc suspension (semilente insulin), and 8% on lente insulin plus crystalline insulin zinc suspension (ultralente insulin). Only 4% of all patients required 2 injections daily, and the average daily dose was 40 units. More than half (55%) of the patients previously required 2 injections of the older preparations daily, whereas with lente insulin 96% were controlled on a single daily injection. The total dose of insulin was decreased by an average of 11 units on transfer from 2 injections of other preparations to one injection of lente insulin. The transfer was controlled by frequent blood sugar estimations, 75 to 200 mg. per 100 ml. being taken as the optimum range. The most satisfactory control was obtained with the lowest dosage. In patients divided according to age and duration of disease no difference in the degree of blood sugar control as between the various groups was found. Patients on a high-calorie diet required a higher dosage of insulin than those with a lower calorie intake, and control was least satisfactory in cases on the highest calorie intake. Urinary sugar excretion was highest in uncomplicated cases, whereas cases with nephropathy had the lowest urinary sugar content, although blood sugar levels were identical in the two groups, suggesting that patients with complications have a high renal threshold for sugar. Ketonuria was most commonly present in patients with a low renal threshold, whereas it was never found in patients with a high threshold.

On reviewing this material after an average period of 18 months it was found that 82% of the patients receiving one injection of lente insulin had remained well on this regimen. Serious hypoglycaemia occurred in 4% of cases and minor reactions in 11%. Local allergic reactions were uncommon and usually disappeared after 4 to 6 weeks. Fat atrophy occurred in 1·4% of cases. The author stresses that while injections should not be given once daily in preference to twice daily at the cost of quality of control, his experience has not confirmed the assertion that patients requiring more than 40 units of insulin a day cannot be controlled by one injection daily. Difficulties were more often due to lability of the disease than to the dose of insulin. *John Lister*

624. **Clinical Investigation of a Hypoglycaemia-producing Sulphonamide.** (Klinische Untersuchungen eines blutzuckersenkenden Sulfonamids)
V. LACHNIT and A. FERSTL. *Wiener Zeitschrift für innere Medizin und ihre Grenzgebiete* [*Wien. Z. inn. Med.*] 37, 363–368, Sept., 1956. 4 figs., 16 refs.

The authors, working at the 2nd Medical Clinic, University of Vienna, have studied the effects on carbohydrate metabolism of *para*-aminobenzenesulphonamido-*iso*propylthiodiazole (IPTD), which has been known since 1942 to produce hypoglycaemia. In healthy volunteer subjects there was a marked flattening of the blood sugar curve after administration of IPTD in daily doses of up to 3 g. This amount was well tolerated, and careful tests for any untoward side-effects failed to discover any changes in the blood picture, any abnormal constituents of the urine, or any signs of impaired liver function. In a series of 12 diabetic patients previously well stabilized on a diet of 1,500 Cal. daily with insulin, the urinary excretion of glucose, which had amounted to 60 to 90 g. in 24 hours, was reduced to 20 to 30 g. daily while they were taking IPTD in a dosage of 2·5 g. on the first 2 days, 2 g. on the next 2 days, and 1·5 g. daily thereafter for periods of up to 6 weeks. The excretion rate of IPTD varied from 45 to 85% of the intake in 24 hours. One patient after taking IPTD for 10 days lost his appetite, while another after 12 days showed a slight degree of retention of " bromsulphalein ", which however disappeared after discontinuation of IPTD. Young diabetics and older patients who had been taking insulin for many years appeared to be refractory to the drug.

The mode of action of IPTD on carbohydrate metabolism is unknown; the authors consider an inhibition of insulinase as a possibility but state that further investigations are necessary. *L. H. Worth*

The Rheumatic Diseases

625 (*a*). **Investigation of the Synergism of *iso*Nicotinic Acid Hydrazide and Cortisone. I. Effect of *iso*Nicotinic Acid on the Metabolism of Cortisone by Liver Tissue**
L. L. WIESEL. *American Journal of the Medical Sciences* [*Amer. J. med. Sci.*] **232**, 412–414, Oct., 1956. 1 fig., 10 refs.

625 (*b*). **Investigation of the Synergism of *iso*Nicotinic Acid Hydrazide and Cortisone. II. Long-term Study of the Synergistic Action of *iso*Nicotinic Acid Hydrazide and Cortisone Acetate in the Treatment of Rheumatoid Arthritis**
L. L. WIESEL, A. S. BARRITT, and C. J. SCHEID. *American Journal of the Medical Sciences* [*Amer. J. med. Sci.*] **232**, 415–418, Oct., 1956. 13 refs.

In the first of these two papers the author describes studies carried out at Brooklyn Hospital, New York, in which it was shown that the addition of *iso*nicotinic acid hydrazide (isoniazid) in concentrations of 0·5 to 15·0 "milligrams per vessel" reduced the destruction of cortisone acetate by rat liver slices *in vitro*. [Few details are given.]

The clinical application of this finding is described in the second paper. In this study isoniazid in doses of 100 to 600 mg. per day, together with cortisone acetate, 37·5 mg. per day, was given by mouth to 39 patients with rheumatoid arthritis, 9 of them being treated for over 2 years, and 24 for over one year. All improved, and a complete remission was obtained in 3 cases. In the remaining 36 cases withdrawal of either drug produced a relapse of disease.

The authors conclude that isoniazid potentiates the action of cortisone by inhibiting the destruction of the latter in the liver.

[This report is unconvincing without further detail.]

Allan St. J. Dixon

626. **Oral Phenylbutazone in the Treatment of Acute Gouty Arthritis**
G. M. WILSON, E. R. HUFFMAN, and C. J. SMYTH. *American Journal of Medicine* [*Amer. J. Med.*] **21**, 232–236, Aug., 1956. 16 refs.

The authors, from the University of Colorado, Denver, describe the results of oral phenylbutazone therapy in 60 acute attacks of gout in 42 males. The response was assessed subjectively by the degree of relief of pain and also objectively by observing the time taken for manifestations of the arthritis to subside. There was complete control of pain within 24 hours in 56 of the 60 attacks, some relief being obtained in 2 to 4 hours. The relief and control of pain were correlated with the attainment of a serum phenylbutazone level of approximately 3 mg. per 100 ml., and this could be achieved by administration of a large initial dose of from 400 to 800 mg. of phenylbutazone. In 47 of 51 attacks all objective evidence of arthritis had resolved within 72 hours, and to attain this result the administration of from 100 to 200 mg. 4 times daily for 3 to 4 days was found to be best. One patient passed a melaena stool 8 days after treatment, and "occasionally a patient complained of mild epigastric burning". Otherwise there were no undesirable side-effects, and it is concluded that phenylbutazone is less toxic than colchicine and that acute gouty arthritis responds dramatically to its use.

J. Warwick Buckler

627. **The Secretor Status of Rheumatic-fever Patients**
A. A. GLYNN, L. E. GLYNN, and E. J. HOLBOROW. *Lancet* [*Lancet*] **2**, 759–762, Oct. 13, 1956. 16 refs.

It has often been suggested that those persons who are susceptible to rheumatic fever have an intrinsic factor unduly sensitizing them to Group-A streptococcal infections of the upper respiratory tract. At the Canadian Red Cross Hospital, Taplow, Buckinghamshire, the authors therefore investigated the relation between the incidence of rheumatic fever and the presence of blood-group antigens (A, B, H, and Lewis) in the saliva and, presumably, the mucous secretions of the throat.

Saliva taken was prepared and titrated against Lewis^a antiserum obtained from immunized rabbits, a heavy white precipitate after one hour's incubation indicating a positive reaction. The reliability of the test was confirmed on saliva from healthy people of known Lewis blood group. The precipitin test for Lewis^a substance and the haemagglutination-inhibition titration test for A and B substances were also carried out with saliva from 115 healthy subjects. Analysis of the results and those of previous workers showed that 3·75% of patients did not secrete A, B, H, or Lewis antigen.

Altogether 450 patients with rheumatic fever, 253 with rheumatoid arthritis, and 460 healthy school-children were studied, the precipitin and/or haemagglutination-inhibition tests being carried out in the cases of rheumatic fever and the precipitin test only in the other two groups. Lewis^a-positive results were obtained in 100 (21·7%) of the healthy controls, 50 (19·8%) of the patients with rheumatoid arthritis, and 124 (27·6%) of those with rheumatic fever. When allowance was made for the 3·75% total non-secretors, the incidence of Lewis-antigen secretors in the healthy controls was 22·6%, in the patients with rheumatoid arthritis 20·6%, and in those with rheumatic fever 28·7%. This difference was significant at the 5% level.

As secretor status is genetically determined, the authors state that these figures support the view that there is a hereditary factor in rheumatic fever. They postulate the possibility of a blood-group linked haptenic material being present in the throat secretions during a streptococcal infection before the onset of rheumatic fever, the haptene being absorbed on the bacteria and becoming completely antigenic.

M. Kendal

Physical Medicine

628. **Clinical Analysis of Static and Dynamic Patterns in Cerebral Palsy with a View to Active Correction**
A. MOLHAVE and P. PLUM. *Archives of Physical Medicine and Rehabilitation* [*Arch. phys. Med.*] **37**, 480–486, Aug., 1956. 5 figs., 15 refs.

The treatment of children with cerebral palsy, especially those with spastic paraplegia, is discussed in this paper from Rigshospitalet, Copenhagen. The postural defects and exercises designed to counteract them are described, special emphasis being placed on attaining correct muscle length—shortening over-stretched muscles and lengthening shortened ones. Before actual walking is attempted the patient is taught to perform the movements necessary for this while on a couch. He is encouraged to perform each particular voluntary movement during manual correction of the faulty posture. The aim of therapy in these cases is to achieve the normal walking of the unhandicapped, in which all muscles are used in the most efficient way. *G. S. Crockett*

629. **The Treatment of Lower-limb Paralysis of Cerebral Origin in Children.** (Traitement des paralysies d'origine cérébrale des membres inférieurs chez l'enfant)
A. BARDIER, M. CAHUZAC, J. NICHIL, and A. OUSSET. *Presse médicale* [*Presse méd.*] **64**, 1683–1685, Oct. 17, 1956. 17 refs.

This is an account of 5 years' experience at a Re-education Centre at Toulouse for the treatment of children with motor disorders of nervous origin, and deals mainly with those affected by paralysis of cerebral origin, of which there were 293. A definite assessment of results is given in 33 cases of paraplegia, 42 of hemiplegia, and 26 of quadriplegia. It was found that the patients with paraplegia were by far the most easy to re-educate.

The aim of treatment was to improve the child from all points of view, and this necessitated close team-work by physicians, teachers, and physiotherapists. The children ranged in age from 29 months to 15 years (mean 8·6 years). In addition to medical treatment the children received speech training and general education compatible with their age and intelligence, the latter in many of these cases being below normal. The methods used in the reduction of spasticity included infiltration of tendons and muscles with local anaesthetic and the rectal administration of curare. From the standpoint of physical medicine there was a concentration on the "muscle-imbalance" theory of postural deformity—that is, that the deformities in spastic children are due to hypertonicity in one group of muscles and hypotonicity in another, and that these can be largely corrected by restoring the balance of tone with suitable exercises. In some cases deformities were corrected by means of plasters, and in others by tendon transplantation and nerve section.

The results of treatment of 42 girls and 39 boys who stayed at the centre for an average period of 11 months are described. Approximately one-third showed great improvement, one-third some improvement, and one-third no improvement. It is clear that valuable work can be done at such a centre.

[The emphasis in this paper on training the child not only to walk but also in other essentials of daily life is good; but the article suffers somewhat from its multiple authorship.] *G. S. Crockett*

630. **The Treatment of Writer's Cramp by Relaxation.** (Traitement de la crampe des écrivains par la relaxation)
J. DE AJURIAGUERRA, J. GARCIA BADARACCO, E. TRILLAT, and G. SOUBIRAN. *Encéphale* [*Encéphale*] **45**, 141–171, 1956. 1 fig., 2 refs.

The authors have sought to adapt two methods of relaxation to the treatment of the condition known as writer's cramp, these being "Jacobson's progressive relaxation" and "Schultz's autogenous training".

The classic writings on writer's cramp are reviewed, with reference to the pathology, aetiology, and treatment, and the mode of application of the methods of treatment mentioned above are described. The aim of the former is to diminish the tonus and so permit use of the limb, while the second method attempts to secure awareness of the symptoms "within the framework of the patient's personality". As writer's cramp is not simply a hypertonic muscular state, but "a dyspraxia of writing on the affective side", Schultz's method appears better adapted to the treatment of the condition by virtue of the relationship it introduces between the therapist and the patient, and also because it permits the more effective destruction of the symptom in the field of consciousness.

[The importance of this review is that it emphasizes the great advantage of giving the patient a part to play in his own treatment and illustrates the improvement which results when the patient's active cooperation is obtained.] *Kenneth Tyler*

631. **Therapeutic Exercises in Management of Paralysis Agitans**
D. J. ERICKSON, E. C. CLARK, D. W. MULDER, C. S. MACCARTY, and B. G. CLEMENTS. *Journal of the American Medical Association* [*J. Amer. med. Ass.*] **162**, 1041–1043, Nov. 10, 1956. 5 refs.

632. **Changes in the Intra-articular Temperature of the Knee with Cutaneous Vasoconstriction and Vasodilatation of the Toes in Normal Subjects**
R. PENNEYS and N. M. SMUKLER. *Annals of the Rheumatic Diseases* [*Ann. rheum. Dis.*] **15**, 241–245, Sept., 1956. 1 fig., 18 refs.

Neurology and Neurosurgery

633. **The Value of the Electroencephalogram in Selected Cases of Subdural Hematoma**
R. C. TURRELL, L. L. LEVY, and E. ROSEMAN. *Journal of Neurosurgery* [*J. Neurosurg.*] **13**, 449–454, Sept., 1956. 3 figs., 3 refs.

It has already been shown that the initial electroencephalogram (EEG), whether taken in the acute, subacute, or chronic stage, is of no value for distinguishing the operative from the nonoperative type of head injury, so far as unilateral subdural haematomata in adults are concerned. Reduction in amplitude, with or without a slow-wave focus, is present with both types of injury. If, however, there is no amplitude reduction with or without a slow-wave focus in a patient with head injury, the chances are that no subdural haematoma is present. If a patient shows focal neurological signs and EEG amplitude reduction on the same side, even without a known history of trauma, a subdural haematoma is probably present on that side.

At the Veterans Administration Hospital, West Haven, Connecticut, the authors studied the EEG in 12 proven cases of unilateral subdural haematoma with ipsilateral hemiparesis, a Grass 8-channel recorder with at least 13 needle electrodes (27-gauge) inserted into the scalp and ear lobes being used. They found that amplitude asymmetry (unilateral voltage reduction) is best shown by short intercepts (bipolar triangulation), next best by reference of all electrodes on one side to the ipsilateral ear, and least well with a common vertex as reference point, which, however, shows seizure activity better than the other two episodes. Seizure activity may be confusing in cases of acute subdural haematoma, but is usually most prominent on the opposite side.

Amplitude asymmetry (reduction of background activity compared with the opposite side) is usually clearest in the temporal and occipital areas; sleep spindles are reduced on the side of the subdural haematoma. Persistence of an ipsilateral amplitude reduction with or without a slow-wave focus strongly suggests a subdural haematoma, even if the patient improves. The pattern of voltage reduction resembles that observed in other conditions, and there may be fluctuation and delay before the EEG shows a final permanent reduction after removal of the irritating substance. *J. L. Standen*

634. **Studies in Myasthenia Gravis: Neonatal and Juvenile Types**
P. TENG and K. E. OSSERMAN. *Journal of the Mount Sinai Hospital* [*J. Mt Sinai Hosp.*] **23**, 711–727, Sept.–Oct., 1956. Bibliography.

The authors draw attention to the two types of myasthenia gravis which occur in children. Neonatal myasthenia (of which 27 cases have been reported to date) occurs occasionally in infants born to mothers suffering from myasthenia gravis and shows itself at birth or very shortly afterwards by symmetrical muscular weakness, particularly of muscles of bulbar innervation, and feeble movement of the limbs, but rarely by involvement of the ocular muscles. This condition, however, is transitory and may last from only a few hours up to 7 weeks; treatment with neostigmine or pyridostigmine is usually required during this period. Among 180 cases of myasthenia gravis diagnosed and treated at the Mount Sinai Hospital, New York, between 1951 and 1955 there were 21 in children, of which 2 were cases of neonatal myasthenia and 19 of juvenile myasthenia. When myasthenia starts in childhood the authors have noted that it may show some variation from the disease in adults, particularly a tendency for the muscular weakness to be more symmetrical, with a high incidence of bilateral symmetrical ophthalmoplegia. They have found that myasthenic symptoms in children respond well to medical treatment and that myasthenic crises are rare, but on the other hand spontaneous remissions are, on the whole, infrequent. *J. W. Aldren Turner*

635. **Myopathy in Sheep. Its Relationship to Scrapie and to Dermatomyositis and Muscular Dystrophy**
F. D. BOSANQUET, P. M. DANIEL, and H. B. PARRY. *Lancet* [*Lancet*] **2**, 737–746, Oct. 13, 1956. 21 figs., 50 refs.

636. **Cerebrospinal Fluid Thrombocyte-agglutinating Substance in Multiple Sclerosis**
I. PERSSON. *A.M.A. Archives of Neurology and Psychiatry* [*A.M.A. Arch. Neurol. Psychiat.*] **76**, 343–354, Oct., 1956. 13 figs., 36 refs.

In disseminated sclerosis plaques often occur around the small veins in the central nervous system and periventricularly. At Nørre Hospital and the Municipal Hospital, Copenhagen, an investigation was undertaken to determine whether changes in the cerebrospinal fluid (C.S.F.) could account for the appearance of plaques at these sites. In 10 cases of disseminated sclerosis blood was taken for a platelet count at the same time as lumbar puncture was performed. About a 5-mm. length of C.S.F. drawn up into a capillary tube was mixed with an equal volume of blood platelet suspension and the thrombocytes were observed in a counting chamber. Control experiments were carried out with partly isotonic saline, 3·8% and 3% sodium citrate solution, which produced agglutinates of 3 to 4 thrombocytes at the most. Greater agglutination of thrombocytes was observed during phases of progression of the disease, when the cell count in the C.S.F. was somewhat increased. The total protein content of the C.S.F. varied. The plasma fibrinogen level also tended to rise with exacerbation of the disease.

It is suggested that during periods of progression the cerebrospinal fluid contains a thrombocyte-agglutinating substance which penetrates into the small veins of the central nervous system, producing thrombi which consist of masses of agglutinated platelets. *I. Ansell*

BRAIN AND MENINGES

637. "Aphasia" in Cerebral Palsy

P. COHEN and H. M. HANNIGAN. *American Journal of Physical Medicine* [*Amer. J. phys. Med.*] **35**, 218–222, Aug., 1956. 6 refs.

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638. Pseudotumor Cerebri. Benign Intracranial Hypertension

L. M. DAVIDOFF. *Neurology* [*Neurology*] **6**, 605–615, Sept., 1956. 18 refs.

Benign intracranial hypertension or pseudotumor cerebri is defined as a syndrome of increased intracranial pressure producing headache and papilloedema, usually without other neurological signs except occasionally paresis of the 6th cranial nerve. The pressure of the cerebrospinal fluid (C.S.F.) is raised, but its constitution is normal and the ventricular system, as judged by encephalographic studies, is also normal. A review of the literature since 1937 showed that several causes have been considered, namely, thrombosis of the lateral or sagittal sinus associated with aural disease, dilatation of the intracranial vascular bed, disturbance of the circulation of the C.S.F., electrolyte disturbances, cerebral oedema, and toxic disturbances due to infection in other parts of the body, but no single one of these suggested causes can account for all the cases.

The author then reports the findings and results in 61 personal cases, including 15 previously described (Davidoff and Dyke, *Amer. J. Ophthal.*, 1937, **20**, 908), seen at the Albert Einstein College of Medicine, New York. In 9 cases there was a clear association with middle-ear or mastoid disease and in 23 evidence of injury or infection elsewhere in the body, but in the remaining 29 cases no apparent cause could be found. In this last group female patients predominated (18) and the maximum incidence was in the 4th decade of life. In all cases there was papilloedema and in all but one a normal ventricular system. In the majority of cases the electroencephalogram was normal; in the 5 cases in which it was not there was an association with infection or trauma. In the author's opinion treatment should consist in subtemporal decompression; 51 of his cases were treated thus, while in 9 cases treatment was by repeated lumbar puncture, fluid depletion, a salt-poor diet, and the administration of acetazolamide. One patient died 2 months after leaving hospital from an unknown cause and post-mortem examination showed the brain to be normal. Four cases were not traced. Of the remainder all recovered from the disease, though the following complications occurred in 6 cases: epilepsy, which developed in 2 cases, was possibly related to trauma or adhesions in the decompression area; one patient developed a subdural haematoma in relation to the decompression 2 months after operation; in another increased intracranial pressure appeared again 6 years after operation but further treatment was refused; in the 5th case the persistently high intracranial pressure was at first unrelieved by subtemporal decompression, but was relieved later by a theco-peritoneal anastomosis; in the 6th case ventriculography showed slight enlargement of the ventricles, but exploration of the posterior fossa revealed no abnormality and the patient remained well thereafter during a follow-up period of 5 years.

The author concludes that in the small number of patients in this series with a history of aural infection or infection or trauma elsewhere in the body mural thrombi in the sagittal or major lateral sinus may have been the cause. In nearly half the cases, however, there was no such history and in such cases, he suggests, the cause may be of a toxic or allergic nature and in women related in some way to menstrual disturbances of electrolyte balance. In general the prognosis is good, the main danger being impairment of vision. *Brodie Hughes*

639. The Cervical Portion of the Vertebral Artery: a Clinico-pathological Study

E. C. HUTCHINSON and P. O. YATES. *Brain* [*Brain*] **79**, 319–331, June, 1956 [received Oct., 1956]. 7 figs., 8 refs.

This paper describes a clinical and post-mortem study of 48 patients dying at Manchester Royal Infirmary of cerebral vascular lesions of various types. At necropsy the cervical portions of the carotid and vertebral arteries were studied by dissection and radiography after the injection of a solution of silver iodide in 15% gelatin. The normal variations of the vertebral artery are briefly described.

The results of the examinations are considered under three headings as follows. (1) Incidence of atheroma of the vertebral artery in the neck. This was found in 19 patients, and varied from a localized plaque with little or no stenosis to diffuse involvement of the artery. In 3 instances the artery was occluded and in each a superadded thrombosis was responsible for the final occlusion. It was not possible to infer the presence of atheroma in the vertebral artery from the appearances of the vessels in the brain, but if the intracerebral and

Neurology and Neurosurgery

633. **The Value of the Electroencephalogram in Selected Cases of Subdural Hematoma**
R. C. TURRELL, L. L. LEVY, and E. ROSEMAN. *Journal of Neurosurgery* [*J. Neurosurg.*] **13**, 449–454, Sept., 1956. 3 figs., 3 refs.

It has already been shown that the initial electroencephalogram (EEG), whether taken in the acute, subacute, or chronic stage, is of no value for distinguishing the operative from the nonoperative type of head injury, so far as unilateral subdural haematomata in adults are concerned. Reduction in amplitude, with or without a slow-wave focus, is present with both types of injury. If, however, there is no amplitude reduction with or without a slow-wave focus in a patient with head injury, the chances are that no subdural haematoma is present. If a patient shows focal neurological signs and EEG amplitude reduction on the same side, even without a known history of trauma, a subdural haematoma is probably present on that side.

At the Veterans Administration Hospital, West Haven, Connecticut, the authors studied the EEG in 12 proven cases of unilateral subdural haematoma with ipsilateral hemiparesis, a Grass 8-channel recorder with at least 13 needle electrodes (27-gauge) inserted into the scalp and ear lobes being used. They found that amplitude asymmetry (unilateral voltage reduction) is best shown by short intercepts (bipolar triangulation), next best by reference of all electrodes on one side to the ipsilateral ear, and least well with a common vertex as reference point, which, however, shows seizure activity better than the other two episodes. Seizure activity may be confusing in cases of acute subdural haematoma, but is usually most prominent on the opposite side.

Amplitude asymmetry (reduction of background activity compared with the opposite side) is usually clearest in the temporal and occipital areas; sleep spindles are reduced on the side of the subdural haematoma. Persistence of an ipsilateral amplitude reduction with or without a slow-wave focus strongly suggests a subdural haematoma, even if the patient improves. The pattern of voltage reduction resembles that observed in other conditions, and there may be fluctuation and delay before the EEG shows a final permanent reduction after removal of the irritating substance. *J. L. Standen*

634. **Studies in Myasthenia Gravis: Neonatal and Juvenile Types**
P. TENG and K. E. OSSERMAN. *Journal of the Mount Sinai Hospital* [*J. Mt Sinai Hosp.*] **23**, 711–727, Sept.–Oct., 1956. Bibliography.

The authors draw attention to the two types of myasthenia gravis which occur in children. Neonatal myasthenia (of which 27 cases have been reported to date) occurs occasionally in infants born to mothers suffering from myasthenia gravis and shows itself at birth or very shortly afterwards by symmetrical muscular weakness, particularly of muscles of bulbar innervation, and feeble movement of the limbs, but rarely by involvement of the ocular muscles. This condition, however, is transitory and may last from only a few hours up to 7 weeks; treatment with neostigmine or pyridostigmine is usually required during this period. Among 180 cases of myasthenia gravis diagnosed and treated at the Mount Sinai Hospital, New York, between 1951 and 1955 there were 21 in children, of which 2 were cases of neonatal myasthenia and 19 of juvenile myasthenia. When myasthenia starts in childhood the authors have noted that it may show some variation from the disease in adults, particularly a tendency for the muscular weakness to be more symmetrical, with a high incidence of bilateral symmetrical ophthalmoplegia. They have found that myasthenic symptoms in children respond well to medical treatment and that myasthenic crises are rare, but on the other hand spontaneous remissions are, on the whole, infrequent. *J. W. Aldren Turner*

635. **Myopathy in Sheep. Its Relationship to Scrapie and to Dermatomyositis and Muscular Dystrophy**
F. D. BOSANQUET, P. M. DANIEL, and H. B. PARRY. *Lancet* [*Lancet*] **2**, 737–746, Oct. 13, 1956. 21 figs., 50 refs.

636. **Cerebrospinal Fluid Thrombocyte-agglutinating Substance in Multiple Sclerosis**
I. PERSSON. *A.M.A. Archives of Neurology and Psychiatry* [*A.M.A. Arch. Neurol. Psychiat.*] **76**, 343–354, Oct., 1956. 13 figs., 36 refs.

In disseminated sclerosis plaques often occur around the small veins in the central nervous system and periventricularly. At Nørre Hospital and the Municipal Hospital, Copenhagen, an investigation was undertaken to determine whether changes in the cerebrospinal fluid (C.S.F.) could account for the appearance of plaques at these sites. In 10 cases of disseminated sclerosis blood was taken for a platelet count at the same time as lumbar puncture was performed. About a 5-mm. length of C.S.F. drawn up into a capillary tube was mixed with an equal volume of blood platelet suspension and the thrombocytes were observed in a counting chamber. Control experiments were carried out with partly isotonic saline, 3·8% and 3% sodium citrate solution, which produced agglutinates of 3 to 4 thrombocytes at the most. Greater agglutination of thrombocytes was observed during phases of progression of the disease, when the cell count in the C.S.F. was somewhat increased. The total protein content of the C.S.F. varied. The plasma fibrinogen level also tended to rise with exacerbation of the disease.

It is suggested that during periods of progression the cerebrospinal fluid contains a thrombocyte-agglutinating substance which penetrates into the small veins of the central nervous system, producing thrombi which consist of masses of agglutinated platelets. *I. Ansell*

BRAIN AND MENINGES

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carotid arteries were atheromatous the chances of the vertebral arteries being similarly affected was considered to be high. (2) Atheroma of the vertebral artery in relation to disease of the carotid artery. A significant degree of atheroma of the carotid artery was seen in 15 cases, in 9 of which atheroma of the vertebral artery was also present. The resultant stenosis varied from moderate narrowing in 2 cases to severe narrowing in 5; in 2 others the final occlusion occurred in a stenosed vessel as the result of an additional thrombosis. In 4 of the cases the atheroma was confined to one vertebral artery. Of the 15 cases of carotid atheroma the internal carotid artery was completely occluded and nearly so in three. (3) Concomitant cerebral and cerebellar infarction. The authors encountered 4 cases in which infarction of a cerebral hemisphere was accompanied by infarction of the cerebellum, which was bilateral in 3.

It is suggested that stenosis of the vertebral artery plays an important part in the development of certain symptoms associated with occlusion of the internal carotid arteries. If the vertebral circulation should fail then the effects of ischaemia would be most marked in the area supplied by the terminal branches of the basilar artery to the hind-brain; it is pointed out that these lesions are not uncommon. Attention is also drawn to the distortion of the vertebral artery caused by bony changes in the spine in cervical spondylosis.

[This important paper should be read by all who are interested in cerebral vascular disease.]

J. MacD. Holmes

640. **Intracranial Haematoma Concealed by Leakage of Cerebrospinal Fluid**

C. CONNOLLY. *British Medical Journal* [*Brit. med. J.*] **2**, 1154–1156, Nov. 17, 1956. 6 refs.

In this paper are described 4 cases in which the signs of post-traumatic intracranial haemorrhage were masked by the decompressive effect of leakage of the cerebrospinal fluid (C.S.F.). It is pointed out that there is displacement of the brain without concomitant compression, and as there is no great impairment of function the presence of a large blood clot may not give rise to clinical signs and symptoms. Further, the escape of fluid may even facilitate haemorrhage within the skull by lowering the intracranial tension.

In 2 of the cases an extradural haematoma was an unexpected finding when a bifrontal bone flap was reflected to carry out intradural repair in cerebrospinal rhinorrhoea. The other 2 patients had otorrhoea, and when this ceased on the 4th and 7th days respectively, signs of cerebral compression developed rapidly. An extradural haematoma was found in one and a combination of subdural and intracerebral haematomata in the other. The author considers that in these 2 cases haemorrhage had ceased long before operation, probably soon after the injury, and that the resultant clot began to compress the brain only when the intracranial pressure rose as a result of the cessation of leakage of the C.S.F. Deterioration in a patient with leakage of C.S.F. may also be due to infection or epilepsy, and the differential diagnosis is briefly discussed. *R. G. Rushworth*

641. **Adverse Cerebral Effects following Acute Haemorrhage in Elderly People**

P. D. BEDFORD. *Lancet* [*Lancet*] **2**, 750–754, Oct. 13, 1956. 12 refs.

Dementia is an uncommon but not rare complication of severe haemorrhage in the elderly, and in this paper 5 cases of extreme dementia are described. During the 6-year period ending December, 1955, a total of 76 patients in the Geriatric Unit at Cowley Road Hospital, Oxford, suffered a severe acute haemorrhage while under observation; of 28 who survived at least 4 weeks, 5, who were considered to be mentally normal before the haemorrhage, were found on recovery to be severely demented. Lesser degrees of dementia in the series as a whole were not assessed, but were "not rare". None of the 5 patients had either a coronary or a cerebral infarction.

The dementia was thought to be the result of cerebral anoxia due to cerebral anaemia following the failure of the homeostatic reflex mechanisms that attempt to preserve the efficiency of the cerebral circulation after acute haemorrhage. Contributory causes were degenerative arterial disease and the "diminished ability in old age to learn new skills . . . and so to compensate for any damage done". To account for the fact that only a proportion of patients become demented the author postulates an individual idiosyncracy. *L. G. Kiloh*

642. **Prolonged Hypothermia in Treatment of Massive Cerebral Haemorrhage. A Preliminary Report**

D. A. HOWELL, J. G. STRATFORD, and J. POSNIKOFF. *Canadian Medical Association Journal* [*Canad. med. Ass. J.*] **75**, 388–394, Sept. 1, 1956. 4 refs.

The authors, at the Montreal General and Queen Mary Veterans Hospitals, Montreal, have employed prolonged hypothermia for the treatment of massive cerebral haemorrhage since this procedure has been shown to reduce the cerebral swelling and also to allow the brain stem to survive the effects of ischaemia longer because of the reduction in metabolic rate. It is believed that death in these cases is always due to a tentorial pressure cone, which causes ischaemia of the vital centres. Hypothermia was achieved by means of fans, ice-bags in the groins and axillae, sponging of the skin with alcohol, and opening of the windows to the Canadian winter, and was maintained for as long as 3 or 4 days. The aim was to keep the rectal temperature between 30° and 32° C. (86° and 90° F.). Particular care was taken to remove secretions from the throat and respiratory tract, the patients being kept in the semi-prone position and tracheotomy being performed when necessary. Chlorpromazine, 50 mg. intramuscularly, was given initially and a further 25 mg. injected whenever the patient shivered or vomited. No fluids were given during the first 48 hours and afterwards they were limited to 200 to 300 ml. a day with, in addition, an amount of fluid equivalent to the previous day's output of urine. By these means a negative water balance was achieved and assisted in the shrinking of the brain.

The case histories are presented of 8 patients, 7 men and one woman, ranging in age from 28 to 72, all of

whom were moribund when treatment was started. Most of them were hypertensive and the treatment produced considerable lowering of the blood pressure. In 6 cases there was a dramatic improvement in the pressure-cone effect, and a " slack brain " was seen in 3 of the 4 cases subjected to craniotomy for removal of the haematoma which, it is recommended, should be evacuated as soon as possible to reduce the residual disability. Of the 8 patients, 2 survived what is usually a fatal state. In 4 cases massive gastric haemorrhage occurred from a gastric ulcer, which seems to be an unexplained complication of the treatment. The selection of cases suitable for this type of treatment is discussed.

[Prolonged hypothermia will surely become more widespread and result in a great reduction in the mortality of this common condition. But the administrative problems raised by the fact that all types of intracranial bleeding are now potentially treatable surgically are enormous.] *G. S. Crockett*

CRANIAL NERVES

643. **The Temporalis Muscle in Facial Paralysis. Report of a Case**
W. C. CONROY. *A.M.A. Archives of Otolaryngology* [*A.M.A. Arch. Otolaryng.*] **64**, 91–97, Aug., 1956. 6 figs., 11 refs.

In cases of inveterate facial paralysis restoration of the " mimetic character " of the facial musculature can be effected completely only by repair of the facial nerve itself. Grafting of peripheral branches to a lower cranial nerve can restore normal tone to the muscles and preserve fairly normal facial symmetry, but emotional response is totally lacking. When these measures have been tried and failed, or when there is long-standing paralysis with atrophy and fibrosis of the muscles, the only treatment is plastic surgery. Many different methods have been tried but none has proved entirely satisfactory, and some of the drawbacks are pointed out by the author. (1) Attempts to animate the forehead and eyelids by transplants of muscle or muscle-fascia may only exaggerate the deformity and any slight movement that is regained does not effectively support the lower lid. For this part of the deformity lateral tarsorrhaphy, with a " face-lift " in the line of the most prominent contralateral crease, narrows the palpebral fissure, raises the eyebrow, and improves the flatness of the forehead. (2) In the lower half of the face the prominent creases are at right angles to the direction of the muscle fibres. Thus the nasolabial groove is a crease at right angles to the levators of the lip, and a line at right angles to the centre of the groove shows the line of force exerted by these muscles; the buccinator muscle pulls the lip backwards and upwards, so modifying this line of force. The transplanting of grafts of fascia lata from the lips to the temporal muscle or masseter do not provide a proper pull in both directions. However, the temporal muscle, with the full extent of its tendon acting under the zygomatic arch, provides a force closely approximating to that of the labial elevator and buccinator and therefore the author, adapting a suggestion made by Batson (*Oral Surg.*, 1953, **6**, 40), uses the muscle belly of the temporal with the anterior half of the tendon, to which he splices the tendons of the extensor longus digitorum of the second, third, and fourth toes, and fixes the free ends of the tendons into the orbicularis oris. A case in which this technique was employed is described, with full operative details and photographs before and after operation.

F. W. Watkyn-Thomas

SPINAL CORD

644. **The Use of Radon for the Location of Spinal Cord Tumours.** (Использование радона для топической диагностики опухолей спинного мозга)
E. N. KRUPIN. *Вопросы Нейрохирургии* [*Vop. Nejrokhir.*] 18–21, No. 4, July–Aug., 1956. 11 refs.

The author describes a method tried by him at the Neurosurgical Clinic, Sverdlovsk Medical Institute, for determining the site of a tumour of the spinal cord which depends on the intrathecal introduction of a mixture of air and radon gas. In a case of spinal block the diffusion of the radioactive gas is held up for some hours at the site of the obstruction and the increased radioactivity at this point can then be detected by means of a counter moved slowly along the vertebral column.

L. Crome

645. **Spinal Cord Involvement in Multiple Myelomatosis**
E. CLARKE. *Brain* [*Brain*] **79**, 332–348, June, 1956 [received Oct., 1956]. 9 figs., bibliography.

Myelomata of the spinal column are frequent in multiple myelomatosis; Batts found radiological evidence of their presence in 70% of cases. Unlike cranial myelomata they often encroach on nervous tissue, and next to root pain, spinal compression is the commonest neurological complication. In addition, lesions other than those due to compression are said to affect the cord.

In this paper from the Postgraduate Medical School of London the author analyses 20 cases and reviews 204 others described in the literature. Frequently the illness begins with signs of compression of the cord or cauda equina due to a spinal myeloma arising from bone (85%); a type of primary epidural myeloma does, however, exist. In the remaining 15% of cases spinal compression begins after the onset of the generalized disease. The evidence concerning indirect involvement of the spinal cord in myelomatosis is very slender and is rejected by the author.

Treatment should be prompt and adequate, its aim being total eradication of the compressing mass, first by surgery and then by radiation therapy. Although the over-all course of the disease may not be influenced, considerable relief from the features of spinal compression are often obtained and are considered well worth while. Only those patients in whom spinal compression develops late in the course of the disease should be denied active therapy. *J. MacD. Holmes*

Psychiatry

646. **Controlled Trial of Meprobamate**
E. D. West and A. F. da Fonseca. *British Medical Journal* [*Brit. med. J.*] **2**, 1206–1209, Nov. 24, 1956. 8 refs.

Meprobamate is another of the new tranquillizing drugs and is chemically allied to mephenesin, having the formula 2-methyl-2-*n*-propyl-1:3-propanediol dicarbamate. In a straight clinical trial on 151 psychiatric out-patients attending St. Thomas's Hospital, London, 4 were much improved and 69 reported some benefit, this being most frequent in those with chronic anxiety and tension states, of whom 36 out of 62 (58%) were improved. The usual dosage was one tablet of 400 mg. three times a day. It was found that increasing the dose beyond this rarely increased the benefit, while it often produced undesirable side-effects. The drug was not so effective in severe anxiety states as in the milder ones.

A double-blind trial was then carried out on 26 patients with anxiety states, each patient receiving meprobamate or inert tablets at alternate visits. Results showed a statistically greater improvement with meprobamate, 21 out of 35 patients deriving benefit, whereas only 12 did so while taking the placebo. In another double-blind trial, carried out on 51 psychoneurotic patients, meprobamate was given alternately on this occasion with sodium amylobarbitone, the latter in a dosage of 1 grain (65 mg.) three times a day, this dose being considered equivalent in therapeutic effect to a 400-mg. dose of meprobamate.

There was no marked difference in result between the two drugs, 10 patients faring better with amylobarbitone and 9 with meprobamate, while 5 declared they slept better with the former and 9 with the latter drug. When irritability was a prominent symptom, however, meprobamate seemed more satisfactory clinically. Side-effects due to meprobamate were slight, only 5 patients showing transient rashes. Some patients taking higher doses of the drug complained of drowsiness without the benefit of further relief of tension.

E. H. Johnson

647. **Comparison of Reserpine and Placebo in Treatment of Psychiatric Outpatients**
J. A. Meath, T. M. Feldberg, D. Rosenthal, and J. D. Frank. *A.M.A. Archives of Neurology and Psychiatry* [*A.M.A. Arch. Neurol. Psychiat.*] **76**, 207–214, Aug., 1956. 14 refs.

Reserpine was given to 27 patients attending the Henry Phipps Psychiatric Clinic, Baltimore, patients who were epileptic, alcoholic, overtly psychotic, mentally defective, or suffering from physical disorders requiring other treatment being excluded. The dosage of reserpine was 0·5 mg. or 1·5 mg. daily for 3 months, a placebo identical in appearance being given to 17 controls. The results were assessed from the patients' answers to 34 questions. Improvement was noted in the 17 controls, the average "distress score" being 33·5 before administration of the placebo and 23·2 afterwards, this difference being significant. The 9 controls who received a placebo as the first treatment for their condition reported reduction in symptomatic distress. Blood pressure and pulse rate in this group were significantly reduced; these values were recorded at 4-week intervals, so the reductions were probably an integral part of the response to a placebo and not to acclimatization to the procedures. No significant improvement was observed in the 14 patients who completed the 3-month course of reserpine, but in 3 there was "favourable response". In this group as a whole distress was relieved for only one symptom—namely, the obsession that "bad thoughts or feelings" kept pushing themselves into the mind.

G. de M. Rudolf

648. **Intracerebral Procaine as Prognostic Test for Prefrontal Lobotomy**
I. W. Scherer and J. F. Winne. *A.M.A. Archives of Neurology and Psychiatry* [*A.M.A. Arch. Neurol. Psychiat.*] **76**, 220–226, Aug., 1956. 3 refs.

The authors attempted to determine: (1) whether behaviour following procaine block of the prefrontal area is a guide to the results of prefrontal lobotomy in psychotic patients; (2) the degree of similarity between the results of psychological tests performed after intracerebral injection of procaine and those performed after prefrontal lobotomy; and (3) whether the changes ascribed to procaine might be due to the other drugs used in the procedure. Of the 18 patients, all of whom were male schizophrenics closely matched for age and stage of disease, 6 received an intracerebral injection of procaine, 6 received the usual preoperative preparation and a subcutaneous injection of procaine, and 6 had no treatment of any kind. Of the first group of 6 patients, 5 later underwent lobotomy.

Immediately after the intracerebral injection of procaine there was a decrease in confusion and delusions, but 3 months after lobotomy there was no reduction in delusions, although confusion was less marked. From the global standpoint, no relationship was observed between clinical improvement following intracerebral injection of procaine and that following lobotomy. Differences between the results of tests carried out after lobotomy and those carried out after procaine block can be explained on the basis of chance. Variations in behaviour within the group of patients given the intracerebral injection of procaine and those in patients receiving the drug subcutaneously did not differ statistically, but the procaine block appeared to have "some disinhibitory effects, possibly related to reduced anxiety".

G. de M. Rudolf

Dermatology

649. **Warts—A Preliminary Survey**
A. BARR and R. B. COLES. *Transactions of the St John's Hospital Dermatological Society* [*Trans. St John's Hosp. derm. Soc. (Lond.)*] 14–23, No. 36, 1956. 2 figs., 6 refs.

Since immunity to virus warts can be induced by repeated inoculation, and if the antigenic stimulus is directly related to the number of warts infecting a patient, then a large number of warts might be expected to resolve more rapidly than single ones. To investigate the validity of this argument a survey was carried out at the Northampton and Kettering General Hospitals of 567 patients with warts, 242 of whom had plantar warts, females being slightly more numerous than males. The sex and site distribution of the warts and the mean number of warts found in each sex and age group are analysed in detail.

Contrary to expectation it was found that multiple warts, treated by a variety of methods, required a longer period before cure was achieved and had been present longer before the patient's first attendance at the clinic than single warts.

[This is a useful and laborious investigation on a sound statistical basis. It is unfortunate that the two figures reproduced are not more adequately explained, failure to indicate the meaning of the abscissa in one of them making it unintelligible.] *S. T. Anning*

650. **Butylphenamide; a New Anti-fungal Agent; Preliminary Studies**
J. D. KRAFCHUK. *Journal of Investigative Dermatology* [*J. invest. Derm.*] **27**, 149–157, Sept., 1956.

Butylphenamide (N-*n*-butyl-3-phenyl-salicylamide) occurs as colourless, non-hygroscopic crystals which, when powdered and suspended in 1% tragacanth solution, can readily be incorporated in various vehicles for clinical use. This paper, from the U.S. Naval Hospital, Vallejo, California, reports the results of its trial use in the treatment of 183 patients suffering from fungus diseases of the skin and certain other common chronic dermatoses. A detailed summary of previous studies on the microbiology, pharmacology, and toxicity of this substance shows that *in vitro* butylphenamide is a highly potent fungistatic and fungicidal compound which compares very favourably with a number of currently used fungicides. It has also been shown to be more active than other preparations when incorporated in ointments, lotions, and tinctures and in the presence of serum. The development of resistance to its action was not demonstrated in an admittedly limited study. In experiments on mice, rats, and rabbits, the compound was found to have no detectable toxic, irritative, or sensitizing properties.

In view of these findings a clinical trial was instituted in which local applications of a 5 or 10% tincture, or a 5% ointment, or a 5% concentration in a water-soluble base was given at random to different cases of fungus infection or chronic dermatosis. Skin punch biopsies during and after treatment showed no changes other than those related to the disease treated, and no abnormality developed in the blood or urine. The tabulated results of treatment of 98 patients with dermatomycoses show that 32 were completely cured and 22 were well except for residual erythema. The best results were obtained in cases of tinea corporis, tinea pedis, and tinea cruris, but even when clinical improvement did not occur there was a marked relief of irritation in many cases. This antipruritic effect was further demonstrated in the treatment of cases of lichen chronicus simplex, atopic eczema, infantile eczema, contact dermatitis, pruritus ani, and otitis externa. Thus of 71 such cases treated, there was complete relief in 11 and considerable improvement in another 25; in 20 cases there was no change, but in only one was the condition made worse.

In a final small group of miscellaneous dermatoses—including psoriasis, pityriasis rosea, verrucae vulgaris, lichen planus, parapsoriasis, molluscum contagiosum, alopecia areata, sycosis barbae, and dermatitis herpetiformis—the drug had no significant effect.

The author considers nevertheless that the results so far warrant further and more extensive trials of butylphenamide. *Benjamin Schwartz*

651. **Relapse in Discoid Lupus Erythematosus Treated with Antimalarial Drugs**
J. ROGERS and O. A. FINN. *A.M.A. Archives of Dermatology* [*A.M.A. Arch. Derm.*] **74**, 387–388, Oct., 1956. 1 ref.

Of 156 patients with chronic discoid lupus erythematosus treated at Dundee Royal Infirmary (University of St. Andrews) since May, 1952, with either mepacrine or chloroquine, those classed as " much improved " and " improved " all relapsed within one year to their pre-treatment status, while out of 41 who were classed as " clear ", only 8 remained free of lesions after 2 years. It was found, however, that when therapy was resumed the condition usually cleared up again, and also that the interchanging of chloroquine for mepacrine or vice versa was effective in some cases. Continued treatment with a small maintenance dose for several months after apparent cure is therefore advised.

Of 24 cases of light-sensitive summer eruption which were treated with chloroquine, the eruption disappeared during the summer in 13, was improved in 7, and was not influenced in 4. In the 13 controlled cases the eruption recurred in the following spring.

[Such a very high relapse rate does not correspond with the abstracter's own experience.]
E. W. Prosser Thomas

Paediatrics

PREMATURITY AND NEONATAL DISORDERS

652. **A Difference in Mortality Rate and Incidence of Kernicterus among Premature Infants Allotted to Two Prophylactic Antibacterial Regimens**
W. A. SILVERMAN, D. H. ANDERSEN, W. A. BLANC, and D. N. CROZIER. *Pediatrics* [*Pediatrics*] **18**, 614–625, Oct., 1956. 3 figs., 11 refs.

In order to determine the most effective prophylactic chemotherapy for premature infants a carefully controlled series of investigations was undertaken at the Babies Hospital, New York. The 192 infants studied were divided into three groups according to birth weight, namely, less than 1,000 g., 1,001 to 1,500 g., and more than 1,500 g., and assigned at random to one of four regimens, all being nursed in incubators. These were: (1) penicillin and sulphafurazole ("gantrisin"), with high humidity; (2) the same drugs, but with moderate humidity; (3) oxytetracycline with high humidity (80 to 90%); and (4) oxytetracycline with moderate humidity (30 to 60%). These conditions were maintained from the time of admission until the age of 120 hours if the infant lived. In the event 97 infants received oxytetracycline and 95 penicillin and sulphafurazole and in each group also approximately equal numbers were nursed in high and moderate humidity. The average age on admission to hospital was 24 hours and treatment was begun about 1½ hours later. Vitamin K was given to both groups in comparable doses (mean 6 g.). The doses of the chemotherapeutic agents were: penicillin 100,000 units daily, sulphafurazole 0·075 mg. per kg. body weight 12-hourly, and oxytetracycline 0·005 g. per kg. 12-hourly, all being given subcutaneously.

Of the 97 infants receiving oxytetracycline, 27 died within 28 days, compared with 60 in the penicillin–sulphafurazole group. The mean age of the 20 infants in the first group who died during the first 120 hours of treatment was significantly less than that of the 46 infants in the penicillin–sulphafurazole group who died during the same period; but after the trial period of 120 hours there was no significant difference between the ages at death in the two groups. The only significant difference in the post-mortem findings in those infants dying during the trial period was the incidence of kernieterus, namely, 1 out of 16 in the oxytetracycline group compared with 12 out of 33 in the penicillin–sulphafurazole group. Among the infants dying after the trial period but before 28 days there was again a marked difference in regard to incidence of kernicterus, no cases being seen in 6 necropsies in the oxytetracycline group but 7 out of 11 being found in the penicillin–sulphafurazole group.

There was no relationship between infection and kernicterus, nor was vitamin-K administration incriminated, since it was given in the same dosage to each group. Careful consideration of all the possibilities leads the authors to the conclusion that the only relevant factor in this outstanding finding was the administration of sulphafurazole. *Wilfrid Gaisford*

653. **Survival of Premature Infants. Classification according to Respiration Rate and Need for Oxygen Therapy**
H. C. MILLER. *Obstetrics and Gynecology* [*Obstet. Gynec.*] **8**, 459–464, Oct., 1956. 5 refs.

The trend of the respiratory rate in premature infants following birth is a better index of survival than the birth weight. No morbidity or mortality was observed among 102 premature infants whose respiratory rates were high or normal during the first hour and subsequently showed no increase. A high morbidity rate and a 25% mortality rate were observed among 52 premature infants whose respiratory rates increased after the first hour. Infants in the lower-birthweight groups had a greater tendency to show an increase in respiratory rates than the infants in the higher weight groups.

The trend of the respiratory rate was of help in judging oxygen needs. No oxygen therapy was required after the first hour. Half of the 52 infants whose rates did increase were given oxygen therapy because they appeared cyanotic. Careful clinical evaluation is still required to determine when oxygen therapy should be instituted or discontinued.—[Author's summary.]

654. **The Significance of Primary Pulmonary Atelectasis in the Newborn.** (Über die Bedeutung der primären Lungenatelektasen beim Neugeborenen)
R. KOEGEL. *Helvetica paediatrica acta* [*Helv. paediat. Acta*] **11**, 283–300, Sept., 1956. 14 figs., 25 refs.

The role of primary pulmonary atelectasis in the causation of 47 neonatal deaths, 35 of which occurred within the first 3 days of life, was studied by the author at the Cantonal Hospital, St. Gallen, Switzerland. The direct cause of death was asphyxia (29 cases), cerebral haemorrhage (8), acute infections (5), haemolytic disease (4), and anencephaly (1). Decrease of the total air capacity by haemorrhage and aspirated fluids vitiated any attempt to assess the extent of the atelectases by measurement of the volume and weight of the lungs at necropsy. Differentiation between primary and secondary atelectasis is essential, and the author gives the microscopical criteria which make this possible.

A relationship appeared to exist between asphyxia (and fatal conditions associated with asphyxia) and secondary atelectasis, but not between asphyxia and primary atelectasis. The author asserts that when alveoli are plentiful and elastic fibres are visible in the alveolar septa the lungs of a newborn infant are mature. He found that in premature infants, and in those with a birth weight under 2,000 g., the bronchi and blood vessels were well developed and contained elastic fibres

in their walls, but the lungs were cellular, with moderate vascularization and with only a few alveolar passages leading to occasional rudimentary alveoli. In full-term infants, and in those with a birth weight over 3,000 g., the capillaries had reached the lumen of the alveolar passages, which communicated with fully developed alveoli. The author was able to demonstrate that the lungs expand the more rapidly after birth, the more advanced their development before birth; and also conversely, that expansion is slower the more premature and underweight the infant. In full-term infants expansion of the lungs was complete at the end of 48 hours, and areas of primary atelectasis diminished rapidly in number and size from then onwards. He suggests, therefore, that this finding can be regarded as physiological until the end of the 2nd day of life, but when these areas occur later, they are pathological and a secondary cause of death; they may be due to failure of the respiratory centre, to malformation of the thorax, or to obstruction of the respiratory passages. In infants born prematurely or of low birth weight expansion of the lung was only one-quarter of the total capacity, that is, about equal to the volume of the alveolar passages alone. After birth development of the alveoli proceeds somewhat more quickly than in the 4 weeks before birth, but respiration can neither expand immature alveoli nor hasten their development. Alveoli do not appear to be essential for survival, for which oxygenation through the capillaries reaching the alveolar passages may suffice. In the author's series it appeared that one-sixth at least of the total air capacity had to be available to ensure survival, since 25% of the infants who survived longer than 2 days had this minimum, and 100% of those who died within 2 days had less than this minimum. In these premature infants primary atelectasis is physiological for a period much longer than 48 hours, and full expansion of the lungs may not be complete until the date on which their full-term delivery would have been due.

The author believes that expansion of the lung usually begins in the periphery of the lobes and spreads towards the hilum. In 50% of his cases of primary atelectasis the atelectatic areas were found only around the hilum, in the remainder being distributed either evenly throughout the lobe or very erratically. Expansion does not appear always to occur simultaneously in all lobes, but it is impossible to determine in which lobe expansion normally first occurs. *E. S. Wyder*

655. **Electrolyte Considerations in Exchange Transfusions for Erythroblastosis Fetalis**

R. P. Bolande, H. S. Traisman, and H. F. Philipsborn. *Journal of Pediatrics* [*J. Pediat.*] **49**, 401–406, Oct., 1956. 8 refs.

The increasing interest in the potassium content of blood used in exchange transfusion for erythroblastosis foetalis is reflected in this study reported from the Children's Memorial Hospital, Chicago, in which 23 infants moderately or severely affected with erythroblastosis foetalis received a total of 26 exchange transfusions between 2 and 72 hours after birth. Stored blood not older than 21 days was used, in which the serum sodium and potassium levels were determined by means of a Weichselbaum flame photometer. The serum potassium level was also determined in each infant before and after the replacement transfusion, the rate of potassium infusion being calculated and expressed in milliequivalents per minute.

On 6 occasions the exchange transfusion was performed with normokalaemic blood and the 4 infants so treated survived and did well. In the remaining 20 instances the blood was hyperkalaemic; of the 19 infants given this blood, 2 suffered cardiac arrest which responded successfully to resuscitation, 2 died from unrelated conditions (ruptured spleen and severe pulmonary emphysema respectively), and 4 died presumably from potassium poisoning. Although there was no correlation between the potassium level in the donor plasma and the level in the infant after transfusion, it was noted that in those infants who died from hyperkalaemia the difference between the potassium level before and after transfusion was considerably greater than in the survivors. [Campbell (*Arch. Dis. Child.*, 1955, **30**, 513) in his study likewise found high potassium levels in those who succumbed.] The rate of potassium infusion, however, appeared to be the critical factor and was higher in the 4 fatal cases than in the others; the reasons, however, are still a matter for speculation. The potential risk to infants from hyperkalaemia in exchange transfusion from stored blood are well illustrated in this paper and the authors [wisely] recommend the use of fresh, warm, donor blood, since it is known that the serum potassium level increases in blood kept in cold storage. *David Morris*

656. **Treatment of Erythroblastosis Fetalis, with Special Reference to Sensitization to Rh-Hr Factors Other than Rh_0**

A. S. Wiener, I. B. Wexler, and G. J. Brancato. *Journal of Pediatrics* [*J. Pediat.*] **49**, 381–393, Oct., 1956. 20 refs.

This paper presents the results of the treatment of 166 babies with erythroblastosis foetalis at the Jewish and Norwegian Hospitals of Brooklyn, New York. Most of the cases were caused by Rh_0 [D] sensitization, but details are also given of a few cases due to hr' [c] sensitization. The method of treatment previously advocated by the authors has been modified in that the blood used for exchange transfusion is relatively fresh (1 to 3 days old) bank blood which is allowed to sediment. From the original mixture of 500 ml. of blood and 120 ml. of A.C.D. anticoagulant solution plasma is then aspirated down to the 450-ml. mark, and the partially concentrated blood is used for the transfusion. Care is taken to see that the volume of blood injected equals the volume of blood withdrawn. The amount of blood injected depends on the severity of the case and the size of the infant; severely affected babies and large infants are given initially 2 units (450 ml.), smaller and less severely affected infants receiving only one unit. Of the 166 infants treated by this technique, 2 died and 3 had neurological complications, giving a combined "mortality" of 3%. In 144 cases treated previously by

exchange transfusion with larger volumes of diluted citrated blood the combined " mortality " was 17·3%.

The usual routine antenatal investigation is designed to detect cases of Rh_0 [D] sensitization only. But the use of test erythrocytes treated with a proteolytic enzyme, papain or ficin, enables less common sensitizations to be detected, and in this way 9 cases of hr′ [c] sensitization were found in the present series. One of these children died before treatment could be started; of the remaining 8 children, 4 were treated by simple transfusion and of these one died, one had neurological sequelae, and 2 survived satisfactorily; the other 4 were treated by exchange transfusion and all recovered without complication. *M. C. G. Israëls*

CLINICAL PAEDIATRICS

657. **Transient Dysproteinemia in Infants, a New Syndrome. I. Clinical Studies**
R. A. Ulstrom, N. J. Smith, and E. M. Heimlich. *A.M.A. Journal of Diseases of Children* [*A.M.A. J. Dis. Child.*] **92**, 219–253, Sept., 1956. 8 figs., 38 refs.

During a period of 18 months 4 infants under 8 months of age with an unusual syndrome of oedema, irritability, pallor, and marked hypoproteinaemia have been subjected to extensive and detailed metabolic and other studies at the University of California, Los Angeles. The hypoproteinaemia was characterized by a uniform reduction in concentration of albumin and all globulin components, and the disease was self-limited and followed by spontaneous recovery. In all cases the over-all nitrogen balance was positive, and the increased urinary excretion of total nitrogen was not the result of a failure of utilization of dietary nitrogen. The plasma protein turnover rates of these infants were increased, and this appeared to be responsible for the low circulating levels of albumin and globulin. The studies are held to suggest that an abnormality in protein metabolism at the cellular level was responsible for the syndrome seen in these infants and that this disturbance was not primarily of dietary origin. *J. M. Smellie*

658. **Copper Deficiency in Infants. A Syndrome Characterized by Hypocupremia, Iron Deficiency Anemia, and Hypoproteinemia**
P. Sturgeon and C. Brubaker. *A.M.A. Journal of Diseases of Children* [*A.M.A. J. Dis. Child.*] **92**, 254–265, Sept., 1956. 33 refs.

A study of 5 infants with hypochromic anaemia accompanied by marked hypocupraemia, hypoferraemia, and hypoproteinaemia as revealed in the laboratory is reported from the University of Southern California, Los Angeles. The case histories, with haematological and other data, are recorded in detail. Aetiologically, it appears that nutritional inadequacy is of prime importance in the pathogenesis of this syndrome, but such factors as reduced body copper content at birth and rapidity of growth must also be considered. One of the objectives in milk processing is to prevent access of copper to the milk, as this has a deleterious effect on storage and flavour. All the 5 infants concerned had been fed exclusively on a milk diet, and therapeutic tests indicated that the various deficiencies can be corrected with an improved diet. The hypocupraemia can be corrected by the oral administration of copper sulphate. *J. M. Smellie*

659. **Chronic Nonspecific Diarrhea in Infants and Children Treated with Diiodohydroxyquinoline**
S. Q. Cohlan. *Pediatrics* [*Pediatrics*] **18**, 424–432, Sept., 1956. 1 fig., 5 refs.

In a preliminary study, 40 infants and children with chronic nonspecific diarrhea, a syndrome characterized primarily by continuous or intermittent unexplained mild diarrhea and often variously diagnosed as celiac disease, starch intolerance, or intestinal allergy, were treated with diiodohydroxyquinoline. Good responses, manifested by subsidence of diarrhea in 1 to 4 days, ability to tolerate a full diet and relief of tenesmus were observed in 29 of 40 cases treated. There were 6 therapeutic failures and response was equivocal in 5 cases. Therapeutic trials consisting of a period of response to diiodohydroxyquinoline with subsequent relapse following withdrawal of medication was observed in 24 cases with three consecutive successful trials in one patient, two trials in each of 10 patients and one trial in each of 13 patients.

A double-blind placebo study in 41 subsequent cases of chronic nonspecific diarrhea resulted in a therapeutic correlation of 53% with 22 cases responding to drug but relapsing on placebo. There were 18 failures including 12 patients who did not respond to drug or placebo, 2 patients who responded to placebo, and 4 who responded to drug but did not relapse on placebo.

The results seem to indicate that diiodohydroxyquinoline is useful as a nonspecific agent which may effect some fundamental mechanism common to nonspecific diarrheas.—[Author's summary.]

660. **Cystic Fibrosis of the Pancreas with Varying Degrees of Pancreatic Insufficiency**
H. Shwachman, R. R. Dooley, F. Guilmette, P. R. Patterson, C. Weil, and H. Leubner. *A.M.A. Journal of Diseases of Children* [*A.M.A. J. Dis. Child.*] **92**, 347–368, Oct., 1956. 4 figs., 26 refs.

The authors describe a series of 17 children seen at the Children's Medical Center (Harvard Medical School), Boston, between 1947 and 1956 in whom a diagnosis of fibrocystic disease of the pancreas had been made on clinical grounds. The duodenal juice was examined on numerous occasions for *p*H, viscosity, and content of trypsin, amylase, and lipase by a variety of methods, which are detailed. In some of the cases the absorption of vitamin A (11 cases) and of gelatin (7 cases) was also studied, and in 14 cases the electrolytes (particularly sodium and chloride) in the sweat were analysed. The series is presented in three groups as follows.

(1) The first group of 4 patients died, the diagnosis being confirmed at necropsy. In the first child the tryptic activity was normal but the viscosity of the duodenal fluid was increased; the second showed

diminishing tryptic activity and an increased viscosity; the third had diminishing tryptic activity from the age of 4½ months until her death at the age of 15½ months; the fourth child showed normal tryptic activity at the age of 5 years, but by the age of 10 both trypsin and amylase content had diminished and examination of the sweat in this case showed an abnormal elevation of the sodium and chloride content; this patient died at the age of 12 years 8 months.

(2) The second group consisted of 6 children, of whom 5 showed elevation of the sodium and chloride level in the sweat, and 5 also increased viscosity of the duodenal juice; in all 6 cases the tryptic activity of the duodenal juice steadily diminished in concentration, finally resulting in complete loss of proteolytic activity in 3 of them.

(3) The third group of 7 children all had tryptic activity within normal limits at first examination. Later a dissociation of enzyme activity took place, so that one or more of the enzymes trypsin, amylase, or lipase became deficient. Vitamin-A absorption tests showed diminished absorption in 3 out of 4 cases and diminished gelatin absorption in one out of 3.

Discussing their findings the authors point out that fibrocystic disease of the pancreas is thus not an "all or none" condition, but that, as these cases show, it is a progressive one. The finding of pancreatic enzyme activity in one or more samples of duodenal juice does not exclude the diagnosis, since it has been estimated that 10 to 15% of all patients with cystic fibrosis show minimal or no discernible enzyme deficiency in the early stages. Once the diagnosis is established the prognosis depends largely on the degree of pulmonary involvement.

H. G. Farquhar

661. **Electrolyte Concentrations in Sweat and Saliva. A Comparison in Patients with Cystic Fibrosis of the Pancreas and Other Conditions**

E. KAISER, R. H. KUNSTADTER, and R. S. MENDELSOHN. *A.M.A. Journal of Diseases of Children* [*A.M.A. J. Dis. Child.*] **92**, 369–373, Oct., 1956. 5 refs.

The authors have investigated the sodium and chloride content of sweat and saliva in a series of children suffering from cystic disease of the pancreas and in a group with unrelated conditions as a control at the Michael Reese Hospital, Chicago. The sweat was obtained by placing the children in a plastic bag for about one hour, and the saliva by means of small cotton pads, furnished with a check-string, placed in the mouth.

It was found that the chloride content of saliva was raised in all young infants as compared with patients in later childhood, the mean value for 14 children without pancreatic disease and under one year of age being 44·7 (range 17·2 to 98·2) mEq. per litre, while that for 17 older non-affected children was 17·7 (range 5·6 to 33·0) mEq. per litre. The mean saliva chloride content of 9 children suffering from cystic disease of the pancreas was 29·9 mEq. per litre. Though this figure is raised it is below the mean figure for infants without pancreatic disease; thus the saliva test is of little value. However, estimation of the chloride content of the sweat showed significant differences. The mean sweat chloride content for 16 infants suffering from conditions unrelated to cystic disease of the pancreas was 21·6 (range 3·1 to 54·2) mEq. per litre and for 9 older children it was 22·5 (range 11·1 to 37·4) mEq. per litre. The mean comparative figures for 9 children suffering from fibrocystic disease of the pancreas was 107·0 (range 68·9 to 186·0) mEq. per litre. The sodium content of the sweat showed a similar higher concentration in children suffering from cystic disease of the pancreas than in non-affected children.

The authors conclude that analysis of the electrolyte content of the saliva is unreliable as a diagnostic method in cystic disease of the pancreas, but they confirm the value of analysis of the sweat electrolyte content as a confirmatory test.

H. G. Farquhar

662. **Primary Atypical Pneumonia in Children.** [In English]

G. STERNER. *Annales paediatrici* [*Ann. paediat. (Basel)*] **187**, 321–339, Oct., 1956. 6 figs., 47 refs.

The author describes the features of primary atypical pneumonia as seen in 148 cases in children aged 10 days to 15 years who were treated at various hospitals in Stockholm during 1953 and 1954.

The diagnosis partly depends on the presence of an epidemic (47% of the present cases occurred in such circumstances) or the exclusion of other known acute pulmonary disease. The most susceptible age is from 7 to 12 years, the sex incidence is equal, and the season of highest incidence in Sweden is from September to January. The incubation period, which could be exactly determined in 22 cases, ranged from 6 to 31 days, with a peak of cases at 14 to 21 days. Usually the onset is acute; in one-third of these cases there was fever only and no other symptoms. Cough was violent in about one-half. Abnormal physical signs were found in 127 cases and radiological changes in the lungs in 147, about one-half of these showing extensive massive infiltration. The general condition usually remained very good. The leucocyte count exceeded 12,000 per c.mm. in 5 cases. The erythrocyte sedimentation rate was high and cold agglutinins (minimum 1:32) were found in 67% of 129 cases tested. Tests for the presence of virus were carried out in 10 cases but the results gave no significant information.

Comparison of the course of the disease in 48 untreated cases or cases in which sulphonamides or penicillin had had no effect, and in 48 given broad-spectrum antibiotics (aureomycin (28 cases), achromycin (10), chloramphenicol (5), or oxytetracycline (5)) for at least 4 days showed that although the temperature and erythrocyte sedimentation rate fell more quickly in the latter group, neither radiological changes in the lung nor the incidence of complications was affected. There were only 2 deaths in the series, one in a child aged 14 months who died 2 hours after admission on the 3rd day of illness and had *Salmonella typhimurium* in the stools, and the other in an infant aged 10 days who also died within a few hours of admission and in whom acute interstitial pneumonia was found at necropsy.

A. White Franklin

Medical Genetics

663. **Essential Familial Hypercholesterolemia and Xanthomatosis. Follow-up Study of Twelve Danish Families**

J. PIPER and L. ORRILD. *American Journal of Medicine* [*Amer. J. Med.*] **21**, 34–46, July, 1956. 1 fig., 10 refs.

During the years 1941–3 Kornerup examined several members of 14 Danish families in which hypercholesterolaemia and xanthomatosis occurred as an inherited disorder. Twelve of these families were re-examined at the First Medical University Clinic, Aarhus, in 1954 by the present authors. Many new cases of the condition (some missed by Kornerup because of wartime difficulties and some in children born since 1943) were discovered and also the development of the disorder in those recognized in the earlier study could be observed. In all, 112 individuals with hypercholesterolaemia were identified, and of these 42 also showed some signs of xanthomatosis; these patients ranged in age from 2 to 79 years.

In general, hypercholesterolaemia without xanthomatosis was the rule in children and young adults, and hypercholesterolaemia with xanthomatosis in older persons, the latter condition showing a tendency to progress with increasing age. On the other hand the hypercholesterolaemia could be recognized in childhood; the serum cholesterol level increased steadily until about the fifth decade of life.

It is concluded that hypercholesterolaemia is inherited as a dominant character, and that the xanthomatosis is determined by the level to which the serum cholesterol has risen and also by the age of the patient. Full details of the investigations and pedigrees of the 14 families are presented. *H. Harris*

664. **The "Carrier" State in Nephrogenic Diabetes Insipidus**

C. CARTER and M. SIMPKISS. *Lancet* [*Lancet*] **2**, 1069–1073, Nov. 24, 1956. 3 figs., 9 refs.

The four families of 5 boys with nephrogenic diabetes insipidus were investigated at the Hospital for Sick Children, Great Ormond Street, London, to determine whether it was possible to detect the female heterozygotes. The histories showed that 3 of the 4 mothers and 3 of the 4 maternal grandmothers always drank about 6 pints (3·4 litres) of fluid a day, but reported no additional intake during pregnancy; in the fourth family an aunt, but not the mother or grandmother, suffered from polydipsia.

Single morning urine specimens from the mothers and grandmothers, who had taken no fluid since 7 p.m. the previous evening, had specific gravities (S.G.) ranging from 1·005 to 1·020, whereas in urine from 39 mothers of other children attending the hospital the S.G. range was 1·012 to 1·031. The urine of other female relatives of the affected boys gave a range of 1·009 to 1·026. Tests on two further similar specimens from the mother and grandmother showed that the mean S.G. for the mothers was 1·006 and 1·018, for the grandmothers 1·007 to 1·016, and for a group of 12 female control subjects it was 1·017 to 1·029. Of 8 specimens from "other female relatives" the S.G. of 6 of them lay between 1·008 and 1·011 and of 2 between 1·032 and 1·034; the variance in this group is significantly greater than in the control group ($P>0.01$), as is the difference between the means for controls and for the grandmothers (that between the controls and the mothers was already significant on the single-specimen test). It is postulated that a mean S.G. of 1·018 in 3 morning specimens differentiates most female heterozygotes, and did so in all these four families; this would be in good agreement with genetic probability. The highest S.G. among these women was 1·026, and it is stated that "some at least of the affected boys can concentrate to over 1·020 if sufficiently dehydrated". One grandmother was known to be the daughter of a man with the condition.

The 4 mothers, 2 young female relatives who appeared also to be heterozygotes, one grandmother, and 12 control subjects (including 8 men) were then tested with 2 milliunits of vasopressin intravenously at the height of a water diuresis. The mean diminution of flow among the mothers and young relatives was less than among the controls ($0.02>P>0.01$), and the grandmother did not respond at all.

[These tests may not always be sufficient to define the females heterozygous for nephrogenic diabetes insipidus, but they are a great advance on reliance on symptoms and single urine tests. They were not used on the largest family recorded (Cannon, *Arch. Int. Med.*, 1955, **96**, 215). More observations on the response to vasopressin and analysis of the serum electrolytes might shed light on the mechanism of the condition which, as Cannon has suggested, may not consist merely in a lack of response of the renal tubules to antidiuretic hormone.] *G. C. R. Morris*

665. **Studies on the Hereditary Disposition to Rheumatoid Arthritis. On the Potential Significance of Other Rheumatic Disorders and Some Other Factors When Judging the Heredity of Rheumatoid Arthritis.** [In English]

U. SEPPÄ. *Annales medicinae internae Fenniae* [*Ann. Med. intern. Fenn.*] **45**, Suppl. 23, 1–63, 1956. 5 figs., bibliography.

666. **Adynamia Episodica Hereditaria.** [In English]

I. GAMSTORP. *Acta paediatrica* [*Acta paediat. (Uppsala)*] **45**, Suppl. 108, 1–126, May, 1956. 17 figs., bibliography.

Public Health

667. **Epidemiological Questions Discussed at the 13th U.S.S.R. Public Health Congress** (Вопросы эпидемиологии на XIII Всесоюзном съезде гигиенистов, эпидемиологов, микробиологов и инфекционистов)
V. M. ZHDANOV. *Советское Здравоохранение* [*Sovetsk. Zdravookh.*] 3–7, No. 5, Sept.–Oct., 1956.

The author reports that in the U.S.S.R. there has been complete, or practically complete, abolition of cholera, plague, smallpox, relapsing fever (typhus recurrens), Gregorev–Shiga dysentery (although a few foci still remain in the south), dracunculiasis, soft chancre, and lymphogranuloma venereum. Malaria, formerly widespread, should soon disappear, while morbidity from typhus, tularaemia, and brucellosis has been reduced to insignificant proportions. In comparison with the pre-war period there has been a marked fall in the incidence of typhoid fever, diphtheria, and dysentery, and in recent years a notable fall in the number of cases of insanity. Influenza and respiratory infections remain, however, important factors in causing temporary incapacity for work, and there has been no fall in child morbidity from measles, pertussis, and scarlet fever, while diphtheria morbidity has only begun to fall in recent months, and that not everywhere. Child mortality from pneumonia, measles, and whooping-cough remains relatively high. In some years epidemic hepatitis, poliomyelitis, and in some parts of the country tick-borne encephalitis have shown a rise in morbidity.

Some deficiencies in the organization of public health measures are then critically examined, the poor quality of anti-epidemic work in a number of places (notably the Central Asian republics) being pointed out. It is felt that generally too much attention has been paid to scarlet fever and too little to measles and whooping-cough. Vaccination against these diseases has not, in comparison with the practice in foreign countries, been sufficiently exploited and in some areas the incidence of diphtheria has increased, while smallpox (introduced from abroad) has also reappeared. The main plans for a campaign against infectious disease are outlined, and malaria, " mosquito fever ", leishmaniasis of urban type, and ankylostomiasis where they are prevalent are to be tackled forthwith. The abolition of mass susceptibility to dysentery, diphtheria, and ascariasis is regarded as important. Gromashevski showed that the site of location of the causal organism in the host, and its closely related manner of spread, determined the epidemiological peculiarities of any infection, had an influence on the characteristics of the invader, and gave some indication of suitable prophylaxis. Pavlovski explained his theory of the innate tendency to focus formation in diseases, indicated the method of its application, and noted that it was receiving considerable attention abroad. Zdrodovski stated that there had been recent experimental support for the view that a considerable proportion of cases of exanthematic typhus were recurrences of previous infection. Discussion of the nature of the epidemic process dealt with both the social and the biological aspects. Foreign contributors are reported to have spoken highly of the work carried out in the U.S.S.R. in the field of virology. Widespread pertussis vaccination (combined) has been begun, and a series of living vaccines against measles are undergoing trial. *R. Crawford*

668. **Influenza Vaccination in a Residential Boys' School. Report to the Medical Research Council Committee on Clinical Trials of Influenza Vaccine**
G. F. C. HAWKINS, L. A. HATCH, and J. C. MCDONALD. *British Medical Journal* [*Brit. med. J.*] **2**, 1200–1202, Nov. 24, 1956. 1 fig., 2 refs.

An outbreak of influenza A occurred in Wellington College, Berkshire, in February, 1956. Of the 664 boys present, 120 had been inoculated in December, 1954, with a vaccine containing influenza virus A and B strains, 100 had been inoculated in November, 1955, with a vaccine containing the A/Eng/19/55 strain, and a further 100 had been inoculated on both occasions. The admission rate to the sanatorium with influenza in these three groups was 12%, 8%, and 2% respectively, compared with 20% in the 344 boys who had not been inoculated. Throat swabs were taken from 73 of the 92 patients with clinical influenza, and influenza virus A was isolated from 44 of them. Forty of the strains were from uninoculated boys and the remaining 4 from boys inoculated in 1954 only. No strains of virus were isolated from boys who had received the 1955 vaccine. Though the investigation did not constitute a controlled trial reasons are given for believing that the above rates are comparable.

It is concluded that some protection still remained from the 1954 inoculations and that a high degree of protection was obtained from the 1955 inoculations, particularly in boys who had also been inoculated a year earlier. The virus A strains isolated during the epidemic resembled the strains (A/Eng/1/54 and A/Missouri/303/52) used in the 1954 vaccine, but differed from the strain (A/Eng/19/55) used in the 1955 vaccine. —[Authors' summary.]

669. **Recent Evolution and Spread of Strains of Influenza-A Virus**
A. ISAACS. *Lancet* [*Lancet*] **2**, 960–961, Nov. 10, 1956. 9 refs.

A large number of strains of influenza-A virus isolated during and between epidemics in various countries in the past 6 years have been compared serologically at the World Influenza Centre, National Institute for Medical Research, London. The author points out that these studies indicate the need to modify the previously held concept that strains of influenza virus isolated in any

particular epidemic, although generally uniform in antigenic composition, nevertheless showed important antigenic differences from strains isolated in preceding epidemics, and that this was the cause of new epidemics every 2 or 3 years.

Most of the strains of influenza-A virus received at the World Influenza Centre during the epidemic of 1950–51 belonged either to the Liverpool or to the Scandinavian-'50 antigenic group. In 1952–3, however, although strains of the Liverpool group were again isolated, other strains appeared which belonged to a group related to, but not identical with, the Scandinavian-'50; this new group was termed the Scandinavian-'53 group, and strains belonging to it have been isolated in many parts of the world since then. In the spring of 1955, strains of a different group, the Eire-'55, were isolated in widely-scattered countries, and meanwhile strains of the Liverpool variety had practically disappeared. In February, 1956, there began to appear in various parts of the world a new group of strains which was named the Dutch-'56. The Eire-'55 group shows some serological relationship with the Liverpool group, and similarly the Dutch-'56 with the Scandinavian-'53. The author discusses the question whether the emergence of these new strains at the same time in different continents is due to a widely occurring simultaneous mutation. He inclines to the view that mutation in antigenic type is an infrequent occurrence and is sometimes accompanied by a capacity for rapid spread. He ventures to predict that the Dutch-'56 strain will become the next dominant antigenic type of influenza-A virus.

J. E. M. Whitehead

670 (*a*). **An Outbreak of Paratyphoid B Infection Simulating Food Poisoning**
M. B. McCann and C. Cross. *Medical Officer* [*Med. Offr*] **96**, 241–246, Oct. 19, 1956. 2 figs.

670 (*b*). **An Unusual Outbreak of Paratyphoid Infection**
C. G. M. Nicol. *Monthly Bulletin of the Ministry of Health and the Public Health Laboratory Service* [*Monthly Bull. Minist. Hlth Lab. Serv.*] **15**, 240–242, Nov., 1956. 2 refs.

An outbreak of paratyphoid infection occurring in north Nottinghamshire and adjacent areas is described by the Medical Officers of Health of the two districts mainly affected (Worksop and Kirkby-in-Ashfield) and by a medical officer of the Ministry of Health who was associated with the investigation. Attention was first directed to the outbreak on August 30, 1955, 2 days after admission to hospital in Worksop of 2 women with suspected food-poisoning; *Salmonella paratyphi* was isolated from the stools. Inquiries pointed to pork products prepared in a food factory in Kirkby-in-Ashfield and retailed in three shops as the possible source of infection; 6 of 9 employees in the Worksop shop were found to be excreting *Salm. paratyphi* B and 3 *Salm. typhimurium*, and *Salm. paratyphi* was recovered from bacon and other products in the factory as well as from members of the staff. Further cases of infection occurred during the following 3 weeks, and by September 24 a total of 261 patients with paratyphoid infection (101 with and 160 without symptoms of food-poisoning) and 25 patients with *Salm. typhimurium* infection (14 with and 11 without symptoms) had been brought to light.

The incubation period was from 12 to 18 or 24 hours, and the symptoms were mainly abdominal discomfort, vomiting and diarrhoea, and moderate pyrexia; 4 elderly patients died, but in most of the others recovery was rapid. Spread within a family was fairly common, but cross-infection outside the family was not demonstrated. Phage typing showed that the strain of *Salm. paratyphi* was "untypable", but gave characteristic reactions enabling it to be recognized with certainty.

Details are given of the administrative action taken. As regards the origin of the onset all three authors consider that no firm opinion can be given, although the medical officer of the Ministry of Health advances the hypothesis that infection entered the factory through one of the pigs brought for slaughter and that this infection was distributed over many pieces of pork.

F. T. H. Wood

671. **The Alastrim Epidemic in the Hague, 1953–1954.** [In English]
M. de Jong. *Documenta de medicina geographica et tropica* [*Docum. Med. geogr. trop. (Amst.)*] **8**, 207–235, Sept., 1956. 22 figs., bibliography.

672. **Use of Poliomyelitis Vaccine under Epidemic Conditions. Report of Outbreak of Poliomyelitis among Navy Personnel and Dependents in Hawaii**
R. S. Poos and N. Nathanson. *Journal of the American Medical Association* [*J. Amer. med. Ass.*] **162**, 85–92, Sept. 8, 1956. 4 figs., 11 refs.

It is claimed that this paper presents the first reported study of mass vaccination of a population during an epidemic of poliomyelitis. The outbreak of the disease was at first concentrated in a single housing area for U.S. Navy personnel, and in spite of certain theoretical difficulties—such as the possible production of post-inoculation poliomyelitis—it was decided to vaccinate the members of the 7,760 families in the Honolulu district while the epidemic was in progress. Over a 6-month period there were 30 cases of paralytic and 23 of non-paralytic poliomyelitis, with 2 deaths; of these 53 patients, 24 were the children of naval families and 29 were Navy personnel and their wives. Analysis of the attack rates showed that in the group of adults with children aged 6 months to 3 years the attack rate was significantly higher than in married adults without children, and was significantly higher in pregnant than in non-pregnant women; there was no significant difference between the attack rate in husbands and that in wives. As a corollary the attack rate in married adults without children was similar to that in unmarried adults.

A review of the findings in a previous epidemic among Navy personnel in Hawaii revealed that the majority of the cases occurred among married subjects and their dependents; accordingly, the vaccination programme in the present outbreak was limited to these groups.

During the period when the vaccination could have been effective there were 23 cases, and among these the attack rate for the paralytic form of the disease was consistently lower among those who were vaccinated than among those who were not; the difference, however, was not statistically significant. No evidence of any provoking effect of the injections of the vaccine was obtained.

The authors state in conclusion that the figures in this epidemic are too small for firm conclusions to be drawn and further study is required. [Nevertheless the authors appear to be on firm ground. Horstmann and her colleagues (*J. clin. Invest.*, 1955, **34**, 1573) have shown by virus isolation and serological studies that the infection rate among household contacts under 15 years may be as high as 100%, and that poliomyelitis in a family setting is, in fact, as infectious as measles.]

H. Stanley Banks

673. **Points in the Planning of Modern Hospitals.** (Некоторые вопросы планировки современных больниц)
L. O. Yurovskiĭ. *Советское Здравоохранение* [*Sovetsk. Zdravookh.*] 20–24, No. 5, Sept.–Oct., 1956. 6 figs., 2 refs.

Writing from the Ukrainian Institute of Architecture the author makes the criticism that in some recently built hospitals there has been architectural over-elaboration at the expense of function. Standardized planning and some faults in present type-projects are then considered. It is recommended that ward sections should have no through traffic, that ward administration rooms and treatment rooms should be so situated as to minimize travel and noise, and that out-patient clinics should not be in the main hospital building since they are liable to disturb the rest and quiet of the in-patients and also to create the opportunity for undesirable contacts. The main hospital building should be in the centre of the site in order to give maximum quiet (an attempt to base a hospital regimen on the conditioned-reflex theory of Pavlov) and the out-patient departments on the same site peripherally near the road, but still within reasonable distance of the special treatment departments (such as that of radiography) in the main hospital.

R. Crawford

674. **The Geokchai Health Education Campaign in Azerbaijan.** (Геокчайское народное движение в Азербайджане)
V. Akhundov. *Советское Здравоохранение* [*Sovetsk. Zdravookh.*] 24–30, No. 5, Sept.–Oct., 1956.

In the Soviet Union preventive medicine is looked to for an ultimate marked reduction in morbidity and mortality, a constant improvement in the productiveness of labour, and increased expectation of life. Great importance, therefore, is attached to the organization of popular movements for education in hygiene and the improvement of local sanitation, particularly in village communities. Such a movement, begun under medical auspices in 1940 in the Geokchai district of Azerbaijan, is described as an example to less progressive areas. The measures taken were those usually applied to backward rural populations, that is, the use of publicity and slogans, the construction of latrines and bath houses, health surveys, and measures for the protection of wells and the disposal of rubbish. The war, together with some lack of local enthusiasm, prevented any proper development of the movement, and further post-war attempts in 1950 to revive such movements apparently met with no greater success.

In 1954, however, the Government and the Party took a more active part in an attempt to revive the Geokchai movement, employing more intensive publicity in the form of lectures and films, more " purposeful direction ", and (what was apparently absent in the earlier movements) medical and surgical teams to treat the population, with specialists provided by the Soviet Ministry of Health to direct the work. The results achieved in Geokchai—a reduction of 13% in total morbidity for 1955—have been circulated to all districts to encourage similar campaigns. In conclusion, persisting defects are discussed and hopes for the future expressed.

R. Crawford

675. **The Hygiene of Food Treated with DDT.** (Гигиеническая харктеристика пищевых продуктов, полученных от растений, обработанных препаратами ДДТ)
S. G. Serebryanaya. *Гигиена и Санитария* [*Gigiena*] 29–36, No. 10, Oct., 1956. 2 figs., 7 refs.

Estimations carried out at the Ukrainian Nutrition Research Institute of the quantity of residual DDT on fruit, vegetables, and grain which had been subjected to various forms of anti-pest treatment have shown that the amount is related to the method used, and in this paper the author makes certain recommendations with a view to minimizing the risk of toxic effects due to the ingestion of DDT on these comestibles.

Apples from orchards treated with 1·5% oily emulsion of DDT were shown to have residual amounts ranging from 3·5 to 5·0 mg. per kg. at time of picking, the corresponding value being 2·5 to 2·7 mg. per kg. when a 2% aqueous suspension was used. If this latter or DDT powder was used all the DDT remained on the skin and could be removed by peeling (but not by washing), but if the oily emulsion was used the interior of the fruit might contain up to 1·7 mg. per kg. It was further found that the DDT content of fruit fell during the first 20 days after treatment and thereafter remained stable. Windfalls were particularly liable to retain a high residual concentration. The author recommends that apples should be peeled before use for culinary purposes and that the trees should be treated only with the powder or aqueous suspension of DDT during the fruit-bearing period.

Cabbages treated with DDT powder or an 0·25% oily emulsion showed residual DDT on the outer 4 leaves, but the heart was free from contamination. However, treatment with concentrations of 0·5 or 1·0% of DDT not only contaminated the heart but also affected the taste. The risk of contamination of the edible portion is naturally greater when the leaves are loose and the heart not yet formed. The author advises that the powder or 0·25% oily emulsion of DDT be used

for cabbage, but only at the transplanting season or after the hearts are fully formed, and that the outer 4 leaves be discarded before marketing.

Winter wheat may be treated with DDT dust (30 to 35 kg. per hectare [about 200 lb. per acre]) as a protection against insects, but a 10% suspension in diesel oil is required to protect against blight. Such treatment if given before the grain forms results in an insignificant residue of DDT in the grain at harvest time, but treatment after the grain is formed leads to a high residue—up to 4·7 mg. per kg. At this stage, however, treatment with DDT powder is permissible.

The author urges that a maximum permitted amount of residual DDT should be stipulated and controlled by laboratory investigations, and that general regulations regarding the treatment of crops with DDT should be drawn up in accordance with the present findings.

Basil Haigh

676. **Contamination of the Air by Micro-organisms and Dust from Clothing and Bedding.** (Одежда и постельные принадлежности как фактор микробного и пылевого загрязнения воздуха помещений)
A. I. SHAFIR. *Гигиена и Санитария* [*Gigiena*] 19–26, No. 9, Sept., 1956. 4 figs., 8 refs.

The author describes a method for estimating the degree of contamination of cloth with bacteria and dust, and reports the results of an investigation of personal clothing and hospital linen and blankets. On the basis of these results he makes recommendations applicable to the manufacture and use of textiles.

The method, which he claims is superior to conventional methods using liquid extracts of shredded cloth, is briefly as follows. The cloth is tightly stretched over a metal ring, as on an embroidery frame, and this ring is then fixed over a cylindrical container 4 cm. deep, in the bottom of which is a Petri dish containing suitable agar medium. In the centre of the circular area of cloth a pin is inserted, and with this as a handle the cloth is raised and then smartly released; this sudden movement releases bacteria which fall on the plate below, in which, after incubation, the colonies can be counted. The manœuvre is repeated 5 times, and consistent results have been obtained.

These experiments have revealed high counts of bacteria and dust in clothing, especially following physical activity. The pockets of trousers were particularly heavily contaminated, and the author suggests hopefully that these should be made detachable and frequently washed. The cleaning of clothes effectively removes large particles (over 2 to 5 μ), but leaves a high proportion of smaller particles. Cloth should therefore be treated by impregnation with a dust-fixing substance which causes aggregation of the particles. For this purpose the most useful preparation is said to be "emulsol" in a concentration of 0·3 to 0·5 kg. per 10 litres of water, one litre being required per kg. of dry cloth. After immersion for 2 or 3 minutes in this solution the cloth is wrung out and dried; the wearing properties of the cloth are not affected. Studies showed that the use of impregnated cloth for hospital bedding greatly reduced the bacterial contamination of the air in hospital wards after bedmaking.

The degree of contamination of the air by personnel can be reduced by the wearing of overalls, which should be made of closely woven cotton or silk material, of "combination" design, and fastened by zip fasteners rather than buttons or laces. Finally, a plea is made for the introduction of air-conditioning wherever a high standard of purity of air is required. *Basil Haigh*

677. **Toxicity of Some Atmospheric Pollutants**
R. E. PATTLE and H. CULLUMBINE. *British Medical Journal* [*Brit. med. J.*] **2**, 913–916, Oct. 20, 1956. 10 refs.

The authors first describe experiments on the effects of air pollutants on animals. A higher proportion of mice died after exposure to a mixture of sulphur dioxide and smoke than after exposure to SO_2 alone. Mice exposed to smoke first and then to SO_2 survived better than those which had not been first so exposed. No evidence could be established regarding the possible absorption of SO_2 by smoke. In further experiments it was shown that large particles of sulphuric acid mist were more toxic to guinea-pigs than small particles, and also that reducing the temperature of the exposure chamber while keeping the particle size constant increased the harmful effects. The animals which succumbed showed bronchial spasm, emphysema, bronchial desquamation, haemorrhagic consolidation, and oedema of the lungs. Experiments on human volunteers showed that some specially susceptible subjects exposed to sulphuric acid mist in a concentration of 10 p.p.m. developed wheezing, coughing, and expectoration, one of them continuing to wheeze for 2 months afterwards. By increasing the particle size a reduced concentration could be made to produce the same effects.

Fumes from diesel engines contain, among other substances, carbon monoxide, nitric oxide, nitrogen dioxide, aldehydes, vanadium, and organic irritants such as acrolein. Experiments showed that the proportions of these substances present in the exhaust of heavy vehicles varied with the running conditions; their toxic effects on small animals produced a fatality varying from *nil* to 90%. In a study of the London fog of January 4 to 6, 1956, the authors found that filter samples were at first alkaline and later acid. Sulphuric acid mist was not an important constituent and the effects on healthy persons could have been due to SO_2 alone. The fog had no apparent effect on guinea-pigs exposed to it.

The authors conclude that "the toxic effects of smog are due to the action of small quantities of pollutants on exceptionally sensitive human beings; the substances concerned are probably, but not certainly, the sulphur compounds".

[This article is packed with important facts relevant to the problem of air pollution.] *John Pemberton*

678. **Benzpyrene and Other Polycyclic Hydrocarbons in the Air of Copenhagen**
J. M. CAMPBELL and J. CLEMMESEN. *Danish Medical Bulletin* [*Dan. med. Bull.*] 3, 205–211, Nov., 1956. 15 figs., 10 refs.

Industrial Medicine

679. **Silage Gas Poisoning: Nitrogen Dioxide Pneumonia, a New Disease in Agricultural Workers**
R. R. GRAYSON. *Annals of Internal Medicine* [*Ann. intern. Med.*] **45**, 393–408, Sept., 1956. 3 figs., 23 refs.

Cases of acute or subacute pneumonitis caused by the inhalation of fumes containing nitrogen dioxide (NO_2) and nitrogen tetroxide (N_2O_4) among farm-workers engaged in handling fresh corn silage (silo-fillers' disease) are stilll rare enough to merit detailed reporting. In this paper are recorded 2 cases—one fatal—which came under the author's care at the Perry County Memorial Hospital, Perryville, Missouri. The clinical picture in both conformed closely to that already recorded in silo workers and factory workers [see *Proc. Mayo Clin.*, 1956, **31**, 189; *Abstracts of World Medicine*, 1956, **20**, 325]. The first case was in a white male farmer aged 66 years who was exposed to yellowish-brown fumes in a silo for 5 to 8 minutes. Despite prompt artificial respiration and continued intensive medical treatment he died 29 hours later. Death was attributed, following necropsy, to acute bronchopneumonia and probable circulatory failure. The other case was that of the farmer's nephew, aged 31 years, who rescued his uncle from the silo. Exposure in this instance was only of 2 or 3 minutes' duration. In this case there was a dramatic response to oxygen, bronchodilators, and antibiotics. Follow-up examination about 9 months later revealed complete recovery and, in particular, there was no radiographic evidence of residual damage to the lungs. Noteworthy points are the shortness of exposure to the noxious fumes, that there is no specific treatment, and that the absolute need is for unremitting detailed attention to preventive arrangements.

The paper includes photomicrographs of lung sections from Case 1 and the radiograph of the acute phase in Case 2; also a review of the literature on silage-gas poisoning and on the industrial and agricultural toxicology of nitrogen oxides. *A. Meiklejohn*

680. **Dermatitis in Coal-miners**
A. ROOK and G. HODGSON. *British Journal of Industrial Medicine* [*Brit. J. industr. Med.*] **13**, 281–286, Oct., 1956. 1 fig., 22 refs.

In a preliminary investigation the clinical pattern of skin disease in coal-miners was compared with that in non-miners by reference to the notes of cases referred by the Ministry of Pensions and National Insurance. Occupational dermatitis had a high incidence between the ages of 30 and 50 years, and the lesions were more common on the legs and groin than at other sites. The facts disclosed by this investigation stimulated a fuller statistical study of the natural history of dermatitis among South Wales coal-miners.

A series of miners from Glamorgan and Monmouth referred to hospital as out-patients were examined by one or two of three dermatologists, and proformas were completed. Only 53 out of 70 proformas were used in the analysis, owing to important omissions in the remainder. Of the 53 cases, 33 were classified as occupational and 20 as non-occupational in origin. The figures that follow refer to the occupational group. More than half the cases occurred in the 40–59 age group. Lesions involving the feet, legs, thighs, or buttocks were present in 21 of the cases. As regards length of employment, 26 miners had worked underground for over 5 years and 15 for over 20 years. The duration of attacks averaged 11·3 months; 14 of the miners had lost over 3 months from work, and one-quarter had lost over a year. A dermatologist was seen within 3 months of onset by 50%, and almost all saw their own doctor within one month. The miners themselves tended to blame " oil " or " dust and liquids " for their dermatitis, these being recognized causes under the National Insurance (Industrial Injuries) Act. The dermatologists suggested trauma, friction, water, dust, and heat as common causes. Secondary infection of the skin was the most important contributory factor, and it is suggested that hypostatic congestion of the lower leg due to impaired venous circulation may aggravate or prolong skin lesions in this area, particularly in older men.
W. K. S. Moore

681. **The Prevalence of Coalworkers' Pneumoconiosis: Its Measurement and Significance**
A. L. COCHRANE, I. DAVIES, P. J. CHAPMAN, and S. RAE. *British Journal of Industrial Medicine* [*Brit. J. industr. Med.*] **13**, 231–250, Oct., 1956. 15 figs., bibliography.

In this paper from the Medical Research Council's Pneumoconiosis Research Unit, Llandough Hospital, near Cardiff, pneumoconiosis of coal-workers is considered in four groups—three related to stages of progress of simple pneumoconiosis where reticular shadowing scattered throughout the lung fields is noted in the radiographs, and a fourth of pneumoconiosis where massive radiological shadows are present. The first three conditions are benign and cause slight disability, whereas the fourth is a progressive disease which shortens life.

The prevalence of the disease was studied in 12 British collieries, where the number of workers ranged from 157 to 1,247. In 8 of these the surface workers were also studied, the numbers of these ranging from 90 to 244. Among the underground workers the incidence of radiological abnormality varied between 20% and 60%, progressive massive fibrosis being present in 10% to 15%. Among the surface workers the incidence was between 20% and 40%, with the incidence of progressive massive fibrosis between 5% and 12%. (These figures are very similar to those obtained in French collieries. Among Belgian coal-workers, on the other hand, the incidence of

progressive massive fibrosis is lower.) The incidence in 1953 had fallen about 5% as compared with 1950–1.

In the advanced stages of progressive massive fibrosis there was a loss of weight, and patients with this condition have, on the average, higher erythrocyte sedimentation rates than those with simple pneumoconiosis. It is pointed out that progressive massive fibrosis develops only in miners who have simple pneumoconiosis, and therefore if the dust concentrations in the mines were lowered sufficiently to prevent the development of advanced simple pneumoconiosis, progressive massive fibrosis could also be prevented. The removal of all tuberculous miners from the mines would also contribute to prevention. *Kenneth M. A. Perry*

682. **Pneumoconiosis of Kaolin Workers**
L. W. HALE, J. GOUGH, E. J. KING, and G. NAGELSCHMIDT. *British Journal of Industrial Medicine* [*Brit. J. industr. Med.*] **13**, 251–259, Oct., 1956. 13 figs., 8 refs.

Kaolin, or china clay, is an aluminium silicate extensively mined in Cornwall by a wet process; it is subsequently dried and put into bags. This is the first convincing account of any lung damage resulting from inhalation of kaolin dust. Six cases are reported, in men aged 44, 67, 44, 39, 73, and 64, who had worked with kaolin for 28, 30, 24, 14, 20, and 43 years respectively, bagging the dry product. They all complained of shortness of breath with some cough. The first patient had pulmonary tuberculosis, and radiological examination showed increase of bronchovascular markings, and nodules scattered throughout the lungs. In Case 2 there was massive shadowing involving apical segments of both lower lobes. The first patient had died, and histological examination of the lung showed nodular lesions of caseous tuberculosis, but some nodules had hyaline fibrosis which may have antedated the tuberculosis and been produced by dusts. The ash from the powdered lung in this case contained large amounts of kaolin dust with an excess of amorphous silica. In a sample of fibrosed lung obtained from a kaolin worker who had died in Georgia, U.S.A., there were large amounts of pure kaolinite dust. The amounts of kaolin found in these cases were of the order of 20 to 40 g. in both lungs. It is suggested that in respect of the presence of such a large amount of dust the condition resembles the pneumoconiosis of coal-workers and is unlike classical silicosis.

Kenneth M. A. Perry

683. **Carcinoma of the Lung in Workmen in the Bichromates-producing Industry in Great Britain**
P. L. BIDSTRUP and R. A. M. CASE. *British Journal of Industrial Medicine* [*Brit. J. industr. Med.*] **13**, 260–264, Oct., 1956. 17 refs.

Carcinoma of the lung occurring in workers in the chromate-producing industry has been recognized as an occupational hazard in Germany and the U.S.A. In 1949 the present authors completed a survey of 724 workers in the British chromate industry, having found one case of carcinoma of the lung, which proved fatal (*Brit. J. industr. Med.*, 1951, **8**, 302; *Abstracts of World Medicine*, 1952, **11**, 139). Since then they have attempted to follow the mortality experience of the remaining 723 workers, and now report their findings. A total of 333 are no longer employed in the industry; of these, 59 had died, 12 from carcinoma of the lung. Of the 390 workers remaining in the industry, 367 were again examined radiologically in 1955 and as a result one further case of carcinoma of the lung, in a man aged 51, was found; in another case the patient is known to be still living. The expected mortality from carcinoma of the lung in this group over this period would have been 3·3; therefore the ratio between actual and expected mortality is 3·6:1. [For the method of statistical analysis the original should be consulted.] In 9 cases death was ascribed to neoplasm at a site other than the lung, and this accords with the expected incidence. The possibility that the increase could be related to place of residence, social class, or smoking habits was considered, but no evidence was forthcoming to suggest any association. From the material available it is calculated that the mean latent period after first exposure to chromate is 21 years, with a standard deviation of 10 years and a standard error of the mean of 3 years. The increase in mortality from carcinoma of the lung found in this survey is in accord with that reported from the chromate-producing industries in Germany and the United States.

Kenneth M. A. Perry

684. **Cancer in Coking Plant Workers**
D. D. REID and C. BUCK. *British Journal of Industrial Medicine* [*Brit. J. industr. Med.*] **13**, 265–269, Oct., 1956. 4 refs.

The number of deaths from cancer and other causes in the coking plants of the National Coal Board during 1949–54 inclusive have been compared with numbers expected on the basis of the mortality experience of another large industrial organization. No general excess of deaths from cancer was found either in the coking plant population as a whole or in particular occupational groups. An excess in the number of cancer of the lung deaths among men who had worked on the ovens was not paralleled by any increase in proportionate cancer of the lung death rates among retired oven workers nor by any difference in occupational exposure between 20 men dying from cancer of the lung and other employees still at work and of the same age. The reasons for this apparent divergence between past experience in similar industries and present experience in N.C.B. coking plants are discussed.—[Authors' summary.]

685. **On the Mechanism of Silica Toxicity**
D. M. JAMES and J. MARKS. *Journal of Hygiene* [*J. Hyg. (Lond.)*] **54**, 342–350, Sept., 1956. 10 refs.

The authors, at the Welsh National School of Medicine and the Central Tuberculosis Laboratory, Cardiff, studied the effect of silicic acid on tissue cultures of leucocytes, on leucocyte respiration, and on the activity of a group of respiratory enzymes. Silicic acid solutions of 1·67, 3·33, and 5 mM concentrations were prepared. In the weakest solution the acid quickly dissociates to the monomeric form; in the others it is present as a

polymer. The weakest solution caused no damage to guinea-pig leucocytes in culture, and depressed their respiration by only 10 to 35% in 6 hours. The stronger concentrations killed the leucocytes within 3 days; the 5-mM solution inhibited respiration after 3 hours, and the 3·33-mM solution after 6 hours.

The same solutions were allowed to act on cytochrome oxidase, succinoxidase, and succinic dehydrogenase in heart muscle, with ascorbate as reducing agent. The weakest solution caused an inhibition of 37%, and the strongest one of 71%, but if the former were allowed to dissociate by standing its effect became progressively less, and dialysed silicic acid caused no inhibition. The effect on the other two enzymes was slight at all concentrations. Polymeric silicic acid also precipitated cytochrome C whilst the monomer did not, and it is suggested that this property is mainly responsible for silica toxicity. *V. J. Woolley*

686. **Threshold Limit Values for 1956**
AMERICAN CONFERENCE OF GOVERNMENT INDUSTRIAL HYGIENISTS. *A.M.A. Archives of Industrial Health* [*A.M.A. Arch. industr. Hlth*] **14**, 186–189, Aug., 1956. 2 refs.

A committee of the American Conference of Governmental Industrial Hygienists carries out an annual revision of the maximum average atmospheric concentrations of a large number of contaminants to which workers may be exposed for an 8-hour working day without injury to health. With the presentation of the revised values for 1956 the warning is reiterated that " threshold limits should be used as guides in the control of health hazards and should not be regarded as fine lines between safe and dangerous concentrations ".

Established values for some 49 new materials have been added to the previous list, while 24 new materials are given tentative values pending further consideration. Threshold limit values are given both as parts of vapour or gas per million parts of air by volume and as approximate milligrammes of dust, fume, or mist per cubic metre of air. *M. A. Dobbin Crawford*

687. **Studies of Ozone Toxicity. I. Potentiating Effects of Exercise and Tolerance Development**
H. E. STOKINGER, W. D. WAGNER, and P. G. WRIGHT. *A.M.A. Archives of Industrial Health* [*A.M.A. Arch. industr. Hlth*] **14**, 158–162, Aug., 1956. 1 fig., 9 refs.

An investigation is reported into the influence upon the toxic effects of ozone on rats of exercise and of preliminary exposure to ozone while at rest. Whereas rats can be exposed daily for months without apparent injury to an atmosphere containing ozone in a concentration of 1 p.p.m. if at rest, rats exposed to a similar concentration of ozone but given exercise in a rotating cage for 15 minutes of each hour died within 6 hours. Such exercise caused no ill-effects to rats in a normal atmosphere. Rats previously exposed to ozone (1 p.p.m.) while resting, however, survived subsequent exposure to ozone with forced exercise, the duration of their survival depending upon the duration of the preliminary exposure. Moreover, rats exposed to ozone in a concentration of 1 p.p.m. for 6 hours without exercise were able to tolerate subsequent exposure to normally lethal concentrations of ozone (7 to 11 p.p.m.) for 4 hours, their lungs showing no gross abnormality at necropsy, whereas those of rats dying after exposure to ozone for the first time at a concentration of 7 to 11 p.p.m. showed oedema and haemorrhages.

This tolerance was developed very rapidly—within 24 hours of the start of the initial exposure—and persisted for 4 to 6 weeks. Even an exposure so brief as one hour induced a slight degree of tolerance.

M. A. Dobbin Crawford

688. **The Action of Oxy-ethylated Polymer Distillate on the Skin and Its Suitability as a Wetting Agent in the Chemical Industry.** (Действие оксиэтилированного полимердестилата на кожу и пригодность его в качестве моющего средства в условиях химической промышленности)
N. S. SORINSON and V. G. SMIRNOVA. *Гигиена и Санитария* [*Gigiena*] 26–29, No. 10, Oct., 1956.

The oxyethylated polymer distillate described here is a mixture of mono- and di-*iso*ethylphenyl polyglycol ethers. It is used as a wetting agent, chiefly for dust suppression in coal mines, and as an emulsifier in textile dyeing. It has the property of lowering the surface tension of water very considerably, which makes it a useful detergent, and with the advantages over soap that it is unaffected by the hardness, salinity, or *p*H of the water, and is more efficient at low temperatures.

The purpose of the investigation here reported from the Institute of Industrial Hygiene, Moscow, was to ascertain if the great potential value of the substance in industry could be fully exploited without risk of toxic effects upon workers. Daily application for 14 days to the skin of rabbits, followed by prolonged observation, revealed no toxic effects locally or systemically. A group of workers used it as a hand cleanser daily for 6 weeks without ill-effect. Complaints of headache, dizziness, and itching of the skin among workers engaged in the manufacture of the substance were traced to the effects of benzol-sulphonic acid and not to the product. In a few men whose work entailed prolonged contact with the product some dryness and itching of the skin did occur. This was similar to the effect of excessive wetting of the skin and was not considered to be a toxic effect. No occupational dermatitis was observed in this group, and they were less liable than others to septic skin conditions.

Experiments carried out to determine the value of this substance as an industrial hand cleanser showed it to be more effective than soap in removing tetraethyl lead, ethyl mercuric chloride, sabin oil, and hexachlorane from the skin, but inferior to soap in its ability to remove mercury. The regular use of the substance resulted in a significant reduction in the number of cases of dermatitis due to urotropin.

It is concluded that this product, far from being hazardous, may by its use actually reduce the risk of dermatitis by virture of its detergent properties.

Basil Haigh

Forensic Medicine and Toxicology

689. **Megimide in the Treatment of Barbituric-acid Poisoning**
A. LOUW and L. M. SONNE. *Lancet* [*Lancet*] **2**, 961–965, Nov. 10, 1956. 2 figs., 11 refs.

The authors describe 24 cases of severe barbiturate poisoning treated at Bispebjerg Hospital, Copenhagen, of which 19 were due solely to barbiturate, while 5 patients had also taken other drugs. All the cases were extremely severe, the blood level of barbituric acid ranging from 3 to 34 mg. per 100 ml., and 7 of the patients died. One patient received combined therapy with " megimide " (β:β-methyl-ethyl-glutarimide; bemegride) and amiphenazole (2:4-diamino-5-phenyl thiazole), amiphenazole only was administered in 3 cases, and the remaining 20 patients were treated with megimide alone. All the patients were given anti-shock treatment. Megimide was administered intravenously in portions of 500 mg. in 100 ml. physiological saline, not more than 1,500 mg. being given at a time and the rate of infusion being about one drop per second; the total dose varied from 375 to 4,000 mg. and 10 of the patients required only one infusion.

The most striking clinical effect of the treatment was the restoration of the reflexes, which tended to become hyperactive. Impaired respiration improved rapidly. The authors had the impression that megimide therapy contributed to the achievement of a state of stable anaesthesia without shock (the " safe state ") in 11 cases, but it did not reduce the period of coma in severe cases since it did not influence the rate of elimination of barbiturates. The changes in the electroencephalogram in 13 cases during treatment are described. Complications were few and included short-lived mild convulsions in 3 cases and a state of increased muscular irritability in a further 3. Vomiting with aspiration of the vomit occurred in only one case, but was followed by " widespread pulmonary changes ". Six patients developed psychic disturbances one to 3 days after regaining consciousness, but these subsided a few days later. The mechanism of action of megimide is discussed.

P. N. Magee

690. **Arousing Effect of Megimide and Amiphenazole in Allypropymal Poisoning**
J. PEDERSEN. *Lancet* [*Lancet*] **2**, 965, Nov. 10, 1956. 2 figs., 2 refs.

In 22 cases of poisoning by a barbituric-acid derivative (" allypropymal ") " megimide " [bemegride] and amiphenazole exerted an undoubted arousing effect; but comparison with 74 control cases of poisoning by the same derivative which were not treated with those substances indicates that the two drugs did not curtail the period of unconsciousness or restore consciousness at higher blood-levels of barbituric acid than in the controls.—[Author's summary.]

691. **Effect of Megimide and Amiphenazole on Respiratory Paresis**
C. CLEMMESEN. *Lancet* [*Lancet*] **2**, 966–967, Nov. 10, 1956. 1 fig., 2 refs.

Between September, 1955, and April, 1956, 70 serious cases of barbiturate poisoning were treated at Bispebjerg Hospital, Copenhagen, with " megimide " (bemegride) or amiphenazole; the first 24 of these cases were described in detail by Louw and Sonne (see Abstract 689). In all the cases there was loss of consciousness and absent or greatly diminished reflexes. The drugs were administered by intravenous drip, consisting of 500 mg. of bemegride in 100 ml. of physiological saline to which was added 150 mg. of amiphenazole in 10 ml. of saline. The rate was about 100 ml. in 30 minutes, the infusion being continued until 300 mg. of bemegride and 30 mg. of amiphenazole had been administered; it was, however, interrupted when distinct reflexes were elicited or in the event of muscular twitching, vomiting, or incipient convulsions. If after a few hours reflex activity had again decreased or had remained absent, infusion of the drugs was resumed.

Respiratory paralysis was present in 7 cases, but was restored during or shortly after the administration of the drugs. Complications included convulsions during administration in 4 cases and temporary mental disturbances several days after treatment in 3 cases, but these complications were not thought severe enough to contraindicate the use of these drugs in cases of total respiratory paralysis.

P. N. Magee

692. **Delirious Psychosis and Convulsions Due to Megimide**
J. KJÆR-LARSEN. *Lancet* [*Lancet*] **2**, 967–970, Nov. 10, 1956. 2 figs., 3 refs.

Among 50 patients treated with " megimide " [bemegride] for acute barbituric-acid poisoning, delirious psychosis dominated by visual hallucinations developed in 15. The frequency of psychosis was greatest after large doses of megimide; and in these cases the latent period between wakening and the onset of psychosis was briefest. Nine of the cases of psychosis occurred among 12 barbiturate addicts. Among the 38 non-addicts there were 6 cases of psychosis. These 6 patients, who had previously been taking barbiturates in therapeutic doses, had remained unconscious for a long time after administration of megimide.

Convulsions occurred during treatment with megimide in half the barbiturate addicts and in half the patients who developed psychoses, but in only a quarter of the non-addicted patients who did not develop psychoses. These psychoses are apparently exogenous reactions provoked by megimide in barbituric-acid habitués. They resemble spontaneous withdrawal psychoses, but there are certain differences.—[Author's summary.]

Anaesthetics

693. **The Cardiorespiratory Dynamics of Controlled Respiration in the Open and Closed Chest**
A. S. GORDON, C. W. FRYE, and H. T. LANGSTON. *Journal of Thoracic Surgery* [*J. thorac. Surg.*] **32**, 431–453, Oct., 1956. 8 figs., 35 refs.

Carefully controlled, comparative tests, performed on both open and closed chest, dogs and human beings, have established the characteristics of the "physiologically ideal" controlled respiration curve on the basis of arterial oxygen saturation, pCO_2 and blood pressure determinations. These characteristics are as follows.

Shape: The curve should have a gradual pressure rise to a short inspiratory plateau, followed by an abrupt expiratory fall to a longer expiratory plateau.

Position: Positive–negative pressure (PNP) provides over-all superior controlled respiration in the closed chest. This is due to the effect of the negative phase in lowering mean airway pressure so that the deleterious effect of the inspiratory positive pressure on cardiac refill (and ultimately on cardiac output and arterial blood pressure) can be compensated for during the expiratory phase. With the open chest, the use of a negative pressure phase provides no significant circulatory benefit and, if excessive, may be deleterious as regards ventilation. IPP breathing is recommended in the open chest, except under special circumstances.

Amplitude: Positive pressure of approximately 15 mm. Hg is required to provide uniform alveolar ventilation. This influences both oxygenation and carbon dioxide elimination. Negative pressure, when used, serves only to lower the mean airway pressure in the closed chest, there avoiding circulatory embarrassment. With the unilaterally open chest the lung can collapse after each inspiratory phase, due to loss of intrathoracic negativity. Pressure-volume studies indicate that slightly more pressure is usually required for adequate reinflation in the open chest than in the closed chest. With a properly shaped curve, a low mean airway pressure can be attained even with these positive pressure phases. The usual PNP range for the closed chest should be approximately 15 mm. Hg to −5 mm. Hg, and the usual IPP range for the open chest should be approximately zero to 16 mm. Hg.

Inspiratory: expiratory ratio: For both PNP and IPP in the open or closed chest, a 1:2 ratio of inspiration to expiration provides optimal ventilation and is least deleterious to the circulation. The duration of inspiratory pressure influences the blood pressure on the basis of the mean airway pressure and the number of heartbeats during the positive phase. Under certain conditions, which we have detailed, it may be advantageous to vary this ratio.

Rate: A controlled respiration rate of 12 per minute was found to be adequate for most adults. For infants and children the rate should be increased and varied according to their age and size.

This curve form compares favorably with the so-called normal airway pressure pattern obtained by use of a large closed circuit reservoir. It can be produced by a time-cycled controlled respiration and resuscitation unit —such a device was used for these studies—and also by manual compression of the anesthesia bag (IPPB) only. —[From the authors' summary.]

694. **The Significance of the Lung–Thorax Compliance in Ventilation during Thoracic Surgery**
W. E. BROWNLEE and F. F. ALLBRITTEN. *Journal of Thoracic Surgery* [*J. thorac. Surg.*] **32**, 454–463, Oct., 1956. 2 figs., 16 refs.

A study was made at the University of Kansas Medical School, Kansas City, to determine the factors responsible for the inefficient ventilation which often accompanies thoracic surgery. To this end lung–thorax compliance (the relationship of airway pressure to volume of gas in the respiratory system) was measured in anaesthetized and conscious patients, with normal and diseased lungs, before, during, and after intrathoracic operations. Conscious patients inhaled, the airway was occluded, and the airway pressure measured with a pressure transducer during voluntary relaxation; after release of occlusion the volume of passively exhaled gases was measured through a pneumotachograph. This was repeated 20 to 25 times, the average flow, expressed as millilitres of gas per cm. H_2O pressure, being taken as the lung–thorax compliance. During anaesthesia the patient was rendered apnoeic by hyperventilation or relaxant drugs and the lungs were inflated with oxygen. After occlusion of the airway the pressure was measured; the occlusion was then released and the passively exhaled gas measured. The volume/pressure values during inflation and deflation (6 to 12 readings) were averaged to give the mean lung–thorax compliance for each factor measured.

In 9 healthy controls (32 readings) the average lung–thorax compliance was 240 ml. per cm. H_2O (range 130 to 400 ml.). In 9 conscious patients with pulmonary disease the average lung–thorax compliance was 140 ml. per cm. H_2O (range 60 to 220 ml.). Measurements in all the above cases were made with the patient supine. In 13 patients undergoing intrathoracic surgery there was a decrease from an average of 170 ml. per cm. H_2O (range 80 to 290 ml.) the day before operation to 110 ml. per cm. H_2O (range 50 to 200 ml.) 5 days after operation. In 11 patients undergoing chest operations lung–thorax compliance decreased from an average of 170 ml. per cm. H_2O (range 90 to 290 ml.) in the conscious state to an average of 47 ml. per cm. H_2O (range 29 to 62 ml.) during anaesthesia, the average decrease being 67%. In 7 anaesthetized patients there was an average decrease of 10% in the lung–thorax compliance on changing from the supine to the lateral position (ranges: 29 to 62 ml.

supine; 33 to 59 ml. lateral). In one very obese woman with heavy, pendulous breasts and anterior abdominal wall an increase of 136% occurred. Of 5 patients in whom the effect of opening the chest was studied an increase in compliance was noted in 4 and a decrease in one. Retraction of the lung (7 cases) produced a decrease in 5, a small increase in one, and no change in the other. Of 5 patients studied to determine if any change in lung–thorax compliance occurred during operation a decrease was found in 4 after the incision had been closed. To determine the range of variation in compliance 59 measurements were made on 13 patients; these showed an average decrease of 44%.

It is concluded that lung–thorax compliance is influenced by various factors, among them disease of the lung or heart, intrathoracic surgery, and alteration in position of the patient. From this it is implied that the pressure and volume of pulmonary inflation must be varied during the course of an intrathoracic operation to produce adequate ventilation. *D. D. C. Howat*

695. **The Electrocardiogram in Hypotensive Anaesthesia**
W. N. ROLLASON and A. R. R. CUMMING. *Anaesthesia* [*Anaesthesia*] **11**, 319–335, Oct., 1956. 8 figs., 26 refs.

In this article from the Hull Group of Hospitals the electrocardiograms (ECG) obtained from 50 patients undergoing hypotensive anaesthesia for general, thoracic, and ear, nose, and throat surgery are described. The patients, whose average age was 47, were thoroughly examined preoperatively, 44 of them being normotensive and 6 hypertensive, and standard, augmented-limb, and chest-lead ECGs, 12 leads in all, were performed.

After premedication, including administration of chlorpromazine in 17 cases, anaesthesia was induced with 2½% thiobarbitone, pethidine, and a relaxant, and maintained in 44 cases with nitrous oxide and oxygen in a semi-closed-circle absorption apparatus, controlled respiration being employed in some cases. In the remaining 6 cases, nitrous oxide, oxygen, and " trilene " (trichloroethylene) were used in a semi-open circuit. The two main hypotensive agents were hexamethonium and trimetaphan, with the addition of chlorpromazine, procainamide, or " hydergine " in 24 cases; the blood pressure, measured by the Riva–Rocci method, was maintained between 45 and 80 mm. Hg in 41 cases and between 80 and 100 mm. Hg in 9 cases. The ECG, including limb leads and leads V1, 3, and 5, was taken after induction, after injection of the hypotensive drugs, after posturing, immediately after operation, and finally one month postoperatively.

The preoperative ECG was abnormal in 20 patients, of whom 5 were hypertensive and 15 normotensive, the abnormalities including signs of left ventricular strain, ST and T depression, and ventricular extrasystoles; 2 of the 5 hypertensive patients had retinopathy and 2 showed left ventricular hypertrophy on radiography. ECG changes after induction of anaesthesia included the disappearance of extrasystoles in some cases, their appearance in others, while ST and T wave depression accompanied the injection of pethidine and relaxant drugs in several cases. After hypotension was induced a persistent tachycardia was seen in 8 cases, and ST and T-wave changes in 35 cases, recovery occurring within 15 minutes in some. The strain pattern in the hypertensive cases reverted towards normal. The postoperative ECG in 11 cases showed smaller change in the ST segments and T waves than had appeared preoperatively, the change was greater in one case, in 3 with a normal preoperative ECG changes in ST and T waves or loss of voltage were present, while in 36 cases no change was seen.

There were 2 deaths in the series from pneumothorax and pulmonary embolism respectively, and one patient refused a postoperative ECG examination. The remainder showed no significant change, and questioning revealed no change in personality, memory, or concentration. The authors discuss the findings and conclude that there is no evidence that hypotensive anaesthesia caused any permanent damage to the myocardium in this series of patients. They suggest the use of electrocardiographic control during hypotensive anaesthesia so that the blood pressure can be raised if myocardial ischaemia occurs.

[The ECGs supporting some of the authors' conclusions are unfortunately not among those reproduced, while the value of the paper is somewhat reduced by the authors' inability to exclude other factors that may influence the ECG under anaesthesia.] *Raymond Vale*

696. **Clinical Hypothermia: a Study of the Icewater Surface Immersion and Short-wave Diathermy Rewarming Technics**
E. BLAIR, H. SWAN, and R. VIRTUE. *American Surgeon* [*Amer. Surg.*] **22**, 869–879, Sept., 1956. 3 figs., 26 refs.

Writing from the University of Colorado, Denver, the authors describe their method of inducing hypothermia as used in a series of 15 patients, 8 children and 7 adults, undergoing intracardiac surgery with temporary total occlusion of the circulation while cooled to temperatures between 26° and 29° C.

Anaesthesia was induced with thiopentone or cyclopropane after pethidine and scopolamine premedication, and maintained with ether. When in surgical anaesthesia the patient was immersed in water at a temperature of 15° to 18° C., tubocurarine being given as necessary to control shivering, and the heart's action observed by continuous monitoring by oscilloscope of the electrocardiogram. Further cooling was obtained by adding ice to the bath with constant stirring till the water reached 0° to 5° C., the anaesthetic agent being then discontinued as cold narcosis took its place. The body temperature was recorded by thermocouple in the recto-sigmoid, and when it had fallen to between 31° and 33° C. the patient was removed to the operating table, dried, and prepared for surgery. It is pointed out that owing to the temperature gradient between the surface layers of the body and the interior, a further " after-fall " of 3° to 5° C. takes place before the body temperature is in equilibrium. Throughout the procedure the patient was manually hyperventilated, at first with anaesthetic mixture, but during the actual operation on the heart with oxygen only. At the conclusion of the operation the patient was rewarmed by

means of diathermy coils, previously placed around the lower half of the body, until the body temperature reached 34° C., the further rise to normal level being allowed to take place spontaneously during the subsequent 4 to 8 hours.

The patients were in the cold bath for periods ranging from 15 to 60 minutes and the " after-fall " of temperature continued for a further 30 to 75 minutes. After a short initial period of peripheral vasoconstriction upon immersion in the cold bath, there was paralysis of the peripheral vessels with dilatation and in some cases a bright pink skin. Thereafter cooling proceeded rapidly as the large volume of circulating blood cooled by the cold water in contact with the skin increased. As this cooled blood travelled through the large internal vessels it likewise stimulated a vasoconstriction which caused disappearance of the pulse; in spite of this the blood pressure could still be measured by intra-arterial manometry, and was shown to be adequate. Although it could not be ascertained with accuracy, it was believed that hypothermic anaesthesia in the majority of these cases was established at about 31° C. The degree of anaesthesia was adequate for the type of operation performed in this series, although some additional curare was occasionally necessary even to position the patient upon the table.

(Details of the cardiovascular effects of hypothermia are not given here since they are to be the subject of a separate paper.) *Donald V. Bateman*

697. **Physiological Measurements during Anaesthesia with " Fluoromar "**

E. GAINZA, C. E. HEATON, M. WILLCOX, and R. W. VIRTUE. *British Journal of Anaesthesia* [*Brit. J. Anaesth.*] **28**, 411–421, Sept., 1956. 8 figs., 17 refs.

In this paper from the University of Colorado Medical Center, Denver, an investigation is reported of the effects of trifluoro-ethyl-vinyl-ether (" fluoromar ") as an anaesthetic agent in animals and human beings. In animal experiments it was found that fewer cardiac irregularities occurred when adrenaline was given with fluoromar than when adrenaline was given alone or with cyclopropane. In the clinical studies 100 patients were divided into 3 groups, each group being anaesthetized by a different technique: Group 1, infants and children in whom an open-drop technique was used; Group 2, adults in whom anaesthesia was induced with thiopentone and maintained with fluoromar in a closed-circle absorption system; Group 3, 12 patients on whom fluoromar was the only anaesthetic agent used. Biochemical investigations were carried out. Anaesthesia could be induced and maintained easily with fluoromar, although induction was slow. The level of anaesthesia was not easy to determine by the usual criteria, and electroencephalographic monitoring was not helpful in determining the patient's physiological state. Hypotension sometimes occurred without warning and was often associated with bradycardia. Respiratory volume was not much affected in light anaesthesia, but was diminished in deeper planes. Some increase in the blood glucose level, bleeding time, and " bromsulphalein " retention was observed after one hour's anaesthesia with fluoromar, but these values returned to normal as quickly as would have been expected after the use of other agents. Blood volume, urea clearance, and blood urea values were not significantly affected. *Ronald Woolmer*

698. **" Fluothane ": a Non-explosive Volatile Anaesthetic Agent**

R. BRYCE-SMITH and H. D. O'BRIEN. *British Medical Journal* [*Brit. med. J.*] **2**, 969–972, Oct. 27, 1956. 4 refs.

" Fluothane " (2-bromo-9-chloro-1 : 1 : 1-trifluoroethane), a non-explosive, volatile anaesthetic agent, is a clear, colourless, heavy liquid, with an odour not unlike that of chloroform. At the Nuffield Department of Anaesthetics, Oxford University, it has been given to volunteers and to 310 patients (aged 7 months to 91 years) for a variety of surgical procedures. There were no deaths under anaesthesia in the series; one patient died 7 days after operation, but death was probably not attributable to the anaesthetic. Administration was by the open-drop method or by an E.M.O. inhaler (Epstein and Macintosh, *Anaesthesia*, 1956, **11**, 83), which was calibrated to deliver known concentrations of fluothane vapour in air. Induction was smooth and pleasant and, in most cases, rapid and quiet. The rate of drop was somewhat faster than with chloroform, but otherwise the same general principles of administration were followed.

Inhalation of 1% fluothane in air produced loss of consciousness, while 2% in air provided a satisfactory level of surgical anaesthesia in most cases, although occasionally 3% was needed for short periods. The drug caused little salivation, even without atropine, and an oral airway was tolerated early. From their experience the authors advise that drugs with a marked depressant action on respiration should not be given within 90 minutes of induction of anaesthesia. Slowing of the pulse rate was common, but this could be counteracted by premedication with atropine. The anaesthetic did not appear to have any effect on cardiac irregularities. A fall in blood pressure was common. Changes in rate or depth of respiration could not be related to the depth of anaesthesia, so that respiratory signs of anaesthesia became meaningless. Respiratory depression, which limited the depth of anaesthesia, could be overcome by assisted or controlled respiration. Relaxants were used with caution in some cases. Neostigmine tended to cause bradycardia, and the authors therefore advise that the preliminary dosage of atropine should be higher than usual. Consciousness returned within 10 minutes of cessation of administration. Nausea and vomiting were rare, shivering and restlessness being the only after-effects noted.

Fluothane is of little value as an analgesic agent, loss of consciousness occurring before there is any appreciable diminution in sensitivity. Injections of adrenaline do not cause ill-effects, and change to ether is rapid and smooth. The drug should be stored in a cool place in amber bottles; tin and aluminium are affected by its decomposition products, while the liquid itself softens rubber temporarily. The authors state in conclusion

that because of its flexibility fluothane may be preferable to trichlorethylene, except for analgesia; it is non-inflammable and can be given by simple methods. Moreover, if it has a high cardiac safety factor, as has been suggested, it compares advantageously with chloroform. *W. Stanley Sykes*

699. **The Human Cardiovascular Response to "Fluothane" Anaesthesia**
M. JOHNSTONE. *British Journal of Anaesthesia* [*Brit. J. Anaesth.*] **28**, 392–410, Sept., 1956. 7 figs., 12 refs.

"Fluothane" (bromo-chloro-trifluoro-ethane), a moderately volatile, nonexplosive, noninflammable, colourless liquid about as potent as chloroform, was tried at the Royal Infirmary, Manchester, as a general anaesthetic for a large variety of operations on 500 patients. It was vaporized from the smaller bottle of a Boyle's machine, the carrier gas being equal parts of nitrous oxide and oxygen at 10 litres a minute. With the plunger fully withdrawn, concentrations of 0·2% to 4% were obtainable with different settings of the control lever, but in the present trial the concentration being given at any moment was known only approximately. In all cases the fluothane was introduced after induction with thiopentone, and anaesthesia was smooth. A concentration of fluothane vapour of 2% to 3% was accompanied by severe hypotension with bradycardia; with concentrations of 0·75% to 1·25% the cardiac depression was much less, but the respiration rate was about 30 per minute. Ventilation was usually adequate and relaxation fair, although not always good enough for intra-abdominal surgery. When D-tubocurarine was given to patients under fluothane anaesthesia severe hypotension occurred, and the patients also seemed hypersensitive to the cardiac inhibitory effects of neostigmine. It is concluded that when full abdominal relaxation is needed it should be obtained with suxamethonium rather than with curare. *Ronald Woolmer*

700. **Utility of "Viadril" in Anesthesia**
C. L. BURSTEIN. *Current Researches in Anesthesia and Analgesia* [*Curr. Res. Anesth.*] **35**, 476–482, Sept.–Oct., 1956. 5 refs.

The author has used "viadril" (21-hydroxy-pregnanedione sodium succinate) in 500 cases, the patients ranging in age from 7 to 95 years. Most of them were admitted to the Hospital for Special Surgery, New York, for orthopaedic procedures; others underwent abdominal and intrathoracic operations at associated hospitals. After a brief survey of the biochemical and physical properties of viadril, the technique of administration is described in detail. In view of the high incidence of thrombophlebitis reported following its injection in a 2½% concentration in water or saline solution, usually into a vein in the elbow, the author tried giving the preparation by intravenous drip in a concentration of 0·1% in 5% dextrose in water. Premedication was the same as that previously used by him for general anaesthesia. The total dosage of viadril ranged from 200 to 2,000 mg. and averaged 500 mg. in one hour. Induction was slow, taking 15 to 20 minutes in a healthy young adult; to overcome this disadvantage 5 to 10 ml. of 2% hexobarbitone was injected intravenously in some cases. Anaesthesia was maintained with nitrous oxide or cyclopropane. Recovery was also very slow, but reflexes were active and respiratory exchange satisfactory.

The author claims that with viadril there was a significant reduction in the amount of supporting anaesthetic agents required. Laryngospasm and bronchoconstriction were not encountered, nor was any case of delirium noted.

Five cases are described in detail. *Michael Kerr*

701. **Transtracheal Resuscitation**
J. J. JACOBY, W. HAMELBERG, C. H. ZIEGLER, F. A. FLORY, and J. R. JONES. *Journal of the American Medical Association* [*J. Amer. med. Ass.*] **162**, 625–628, Oct. 13, 1956. 3 figs., 12 refs.

Respiratory obstruction may occur as a complication of general anesthesia. Usually this can be treated by simple measures. If these are not effective, endotracheal intubation or tracheotomy should be performed. If these cannot be done for any reason, transtracheal insufflation of oxygen may be utilized as a stopgap measure. Oxygenation can be maintained by this technique for periods of 30 minutes or longer. Within this time skilled help can usually be obtained for definitive treatment of the respiratory obstruction. It is not recommended that transtracheal resuscitation be used as a substitute for endotracheal intubation or tracheotomy, but it can be of value for a relatively brief period for the prevention of death from anoxia.—[Authors' summary.]

702. **Control of Postoperative Vomiting with "Marezine": a Double Blind Study**
D. C. MOORE, L. D. BRIDENBAUGH, V. F. PICCIONI, P. A. ADAMS, and C. A. LINDSTROM. *Anesthesiology* [*Anesthesiology*] **17**, 690–695, Sept.–Oct., 1956. 7 refs.

A double-blind investigation of the anti-emetic properties of "marezine" (cyclizine lactate) was carried out at the Mason Clinic, Seattle, Washington. The control solution, a solvent, and the active solution containing 50 mg. of marezine per ml., were preserved in identical containers, the contents of which were unknown to the clinic staff until the end of the study. Altogether 276 patients received the control solution and 273 the active solution. There was no special selection of patients and no alteration was made in the routine use of drugs before and after operation. An intramuscular injection of 1 ml. of the control or active solution was given immediately before and immediately after operation, and again every 4 hours for 4 doses.

Results were assessed from the patient's replies to questions concerning the frequency of vomiting and the character of the vomit and from the notes and comments of the nursing staff, vomiting being defined as emesis of 50 ml. or more. It was found that 77 (27·9%) of the patients receiving the control solution vomited, compared with 41 (15%) of those receiving marezine.

Michael Kerr

Radiology

703. **The White Cell Count and Exposure to Radiation Hazards. The Significance of Leucocyte "Warning" and "Rejection" Levels in the Younger Age Groups**
F. M. TURNER. *British Journal of Industrial Medicine* [*Brit. J. industr. Med.*] **13**, 277–280, Oct., 1956. 11 refs.

[This is an important contribution to the literature, which is best summarized in the author's own words, as follows.]

"An analysis has been made of the blood counts of 1,897 new entrants [to the Atomic Energy Research Establishment, Harwell] during the period July 1, 1952, to June 30, 1954, to determine the number with counts below 'warning' and 'rejection' levels in various age groups. The number of individuals with neutrophil counts below these levels was found to be higher in the 16- to 19-year age group than in the older groups. There were also more warnings and rejections in all groups attributed to low neutrophil counts than to low leucocyte or lymphocyte counts. An investigation into the distribution of age groups according to season of the year revealed that a higher proportion of apprentice age personnel began employment at the end of the school year, which coincides with the season at which blood counts are known to reach their lowest level.

"The adoption of lower standards for warning and rejection levels of neutrophil counts is recommended."

[The original paper should be consulted for details of the findings, which are set out in 7 tables.]

I. G. Williams

RADIOTHERAPY

704. **Cobalt-60 Teletherapy for Palliation of Carcinoma of the Thoracic Esophagus**
T. F. MEANEY and R. A. HAYS. *Cleveland Clinic Quarterly* [*Cleveland Clin. Quart.*] **23**, 245–250, Oct., 1956. 3 figs., 4 refs.

Since in most cases oesophageal carcinoma has already metastasized when diagnosed, treatment is primarily palliative, to relieve obstruction. For this purpose teletherapy with radioactive cobalt (^{60}Co; equivalent to x rays at 3 million volts) has been in use at the Cleveland Clinic, Ohio, since 1954, and with a rotational technique since 1955. A total of 12 cases of carcinoma of the thoracic oesophagus have been treated; in all of them the lesion was extensive or the patient unfit for surgery. Post-irradiation radiological examination was achieved, and in some of these a normal mucosal pattern was seen at the site of the tumour. There was no mortality due to the irradiation, and negligible morbidity. In one patient, however, the disease progressed in spite of treatment. Some details of 3 cases are given, and radiographs are reproduced. The authors consider that high-voltage irradiation is a striking advance over ordinary "deep" x-ray therapy, a higher tumour dose being achieved with much less systemic upset and insignificant skin reactions. It is the treatment of choice when surgery is ruled out. *J. Walter*

705. **Effect of Radiotherapy on Bone-marrow in Ankylosing Spondylitis**
J. W. STEWART and S. DISCHE. *Lancet* [*Lancet*] **2**, 1063–1069, Nov. 24, 1956. 12 figs., 18 refs.

The results of bone-marrow examination in 28 untreated cases of ankylosing spondylitis are reported. In 3 cases the peripheral blood showed mild hypochromic anaemia, the blood-counts of the remainder being within normal limits. The bone-marrow was hypercellular in 39% and of normal cellularity in the remainder. An increase in the number of lymphocytes and/or monocytes was observed in 79%. In only one case was there a plasmacytosis.

The effect of irradiation of bone-marrow to a dose of 1,020–1,640 r is to cause aplasia, and this was observed in all the cases in which the marrow was examined from 2 days to 6 months after the end of treatment. Examination of the marrow from 15 months to 14 years after treatment showed that regeneration is usually incomplete. Seven of 10 marrows so examined showed aplasia or hypoplasia. Examination of bone-marrow distant from the treatment areas during the 6 months following completion of radiotherapy revealed only transient changes. These were hyperplasia of erythroid precursors and hypoplasia of cells of myeloid and lymphoid series. When examination was made more than 6 months after the end of treatment, the findings were similar to those in patients who had not previously received radiotherapy.—[Authors' summary.]

706. **Betatron Therapy in Advanced Carcinoma of the Urinary Bladder**
J. J. CORDONNIER and W. B. SEAMAN. *Journal of Urology* [*J. Urol. (Baltimore)*] **76**, 256–262, Sept., 1956. 6 refs.

This paper from Washington University School of Medicine, St. Louis, Missouri, describes the results of the treatment of 17 patients suffering from advanced carcinoma of the urinary bladder by means of betatron therapy. The tumours were graded histologically [but no mention is made of clinical staging in this series, except the statement that "no case was included in the series in which the possibility of radical cure by either surgical or conservative means was deemed possible. In every case treatment was instituted with the full realization that the outlook was very poor and that the possibility of cure was almost *nil*"].

Tumour dosages of 4,700 to 7,500 r were delivered to the bladder and whole pelvis over a period of 30 to 40 days, three entrance ports being employed. In 10 of the cases at follow-up cytoscopic examination deep

biopsy of the bladder wall was performed at the site of the previous tumour, even in the absence of any apparent abnormality. [In view of the high dosages administered this procedure is fraught with danger and one to be discouraged because of the risk of precipitating necrosis.]

The incidence of complications was extremely high; they included severe diarrhoea, irradiation cystitis (necessitating diversion of the urinary stream in 2 cases), spontaneous perforations of the bladder, and sub-phrenic abscess. Major gastro-intestinal complications were observed in 9 of the patients, surgical intervention being required in 6, in 3 of whom intestinal perforation was found. Of the 17 patients, 8 died within 6 months of treatment and only 4 survived longer than 14 months, the disease in 2 of these being again active. The incidence of complications in this series was such that the authors conclude that radiotherapy for advanced carcinoma of the bladder should aim at palliation only. They consider that radical surgery offers the best possibility of cure in patients with lesions localized to the bladder [but this view is by no means generally accepted by those experienced in treating malignant disease of the bladder].

Norman Mackay

RADIODIAGNOSIS

707. Paraphyseal or Colloid Cysts of the Third Ventricle

H. W. SLADE, N. M. GLAZER, and H. HAUSER. *Radiology* [*Radiology*] **67**, 351–358, Sept., 1956. 8 figs., 14 refs.

The presence of intermittent symptoms of increased intracranial pressure without localizing evidence is characteristic of anterior third-ventricular tumours, of which the most common is the colloid or paraphyseal cyst. The first case was reported by Wallman in 1858 and up to the present 119 cases have been described in the literature. The first successful removal was accomplished by Dandy in 1921, since when the number of such tumours removed surgically has steadily increased.

The paraphyseal origin of these cystic tumours was first suggested by Sjövall in 1909. The paraphysis is a glandular structure found in some of the lower vertebrates; in the human embryo it appears about the 75th day of gestation and normally disappears shortly thereafter. In some individuals, however, remnants of the gland persist and slowly enlarge, presumably by retention of products of the secreting epithelial cells. As the structure grows it projects downwards into the third ventricle and to a varying extent also upwards and forwards. It is enfolded by the layers of the tela as it starts downwards, and this has given rise to the belief that it should be called a cyst of the choroid plexus. Although it is a benign lesion, the sudden occlusion of both interventricular foramina by the growth can result in sudden death. Symptoms have included visual disturbances, fainting, dizziness, staggering, weakness in the arms and legs, headache, nausea, and vomiting. Objectively there may be no abnormality, but papilloedema or optic atrophy may occur. Personality changes of an intermittent nature sometimes occur and often lead to a diagnosis of psychoneurosis.

In this paper 5 cases seen at Cleveland (Ohio) City Hospital are described. Plain radiography of the skull usually reveals no abnormality. Accurate preoperative diagnosis depends on pneumographic and *x*-ray contrast studies. Because of the location of the cyst in the roof of the third ventricle many different appearances are possible, depending on the degree of obstruction. These include: (1) dilatation of the lateral ventricles, with absence of air in the third ventricle; (2) dilatation of the lateral ventricles with a bulge in the floor of the third ventricle and absence of air in that structure; (3) dilatation of the lateral ventricles and of the foramina of Monro, with a filling defect in the anterior portion of the third ventricle; (4) dilatation of the ipsilateral ventricle by occlusion of only one foramen of Monro, with no passage of air from one lateral ventricle to the other, or to the third ventricle, and without visualization of the third ventricle; (5) symmetrical dilatation of the lateral ventricles, which have been filled from one side alone, with absence of the shadow of the septum pellucidum; (6) dilatation of both lateral ventricles, with bulging of the septum pellucidum to one side. All these are ventriculographic findings, but another appearance is occasionally seen, namely, filling of the cyst with air during pneumoencephalography. Competent radiologists and neurosurgeons have failed to interpret this appearance correctly and have confused the air-filled cyst with a dilated third ventricle. The mechanism of entry of the air into the cyst is obscure, but most probably perforation of its wall takes place.

J. MacD. Holmes

708. Experience with a New Contrast Medium (Hypaque) for Cerebral Angiography

J. E. WHITELEATHER and R. L. DESAUSSURE. *Radiology* [*Radiology*] **67**, 537–543, Oct., 1956. 4 figs., 5 refs.

Experience with a new contrast medium, " hypaque " (sodium diatrizoate), for cerebral angiography is reported from the University of Tennessee and the Baptist Memorial Hospital, Memphis. In preliminary animal experiments the effects of hypaque sodium 50% and " urokon " sodium 30% were compared with those of " diodrast " (diodone) 35% by repeated carotid injections in dogs. Every effort was made to follow the same procedure and to use the same quantities of contrast medium for each injection. The authors summarize their findings as follows: " Blood–brain-barrier injury was demonstrated by trypan blue . . . but this was not found to be as reliable as a system of grading the respiratory effects and neuromuscular reactions. Hypaque sodium proved to be no more irritant or toxic than diodrast but provided superior contrast. There were fewer side-effects than with diodrast, such as nausea, allergic reactions, and subjective complaints. Urokon sodium 30% was fairly well tolerated, but did produce evidence of blood–brain-barrier damage in lesser amounts than hypaque sodium. Urokon sodium almost uniformly caused convulsions or strong tonic muscular contractions, with severe blood–brain-barrier damage. In 300 cerebral or vertebral angiographic studies with hypaque sodium in patients of all ages, there were no

untoward effects directly traceable to the medium. Radiographic contrast has been uniformly better than with diodrast, with one-half the dosage. The diagnostic quality of the films was unquestionably better and the interpretation of the radiographs was easier ".

A. Orley

709. **Effect of Unabsorbed Radiographic Contrast Media on the Central Nervous System**

F. L. DAVIES. *Lancet* [*Lancet*] **2**, 747–748, Oct. 13, 1956. 3 figs., 11 refs.

This [highly condensed] report from the Middlesex Hospital, London, is based on observation of the effects of myelography on 119 patients. The total number of myelograms was 125, " myodil " being used for 124 and iodized oil for one. On the average, 5 ml. of contrast medium was injected, lumbar puncture being performed in 119 cases and cisternal puncture in 6; in 2 cases the injection was given by both routes.

There was an immediate reaction to the injection of myodil in 56 cases, the reaction being severe in 47 and mild in 9. In a further 14 cases " the symptoms had persisted or had developed later and were found when the patients were examined a year or more after myelography ". Of these chronic symptoms attributed to myodil, continuous pain and cramp in the legs were the most frequent. Operative and post-mortem findings revealed evidence of permanent damage to the pia-arachnoid causing obstruction of the subarachnoid space. The author states that the large quantities of residual contrast medium present in the cranium and spinal canal many years after injection indicate a slow rate of absorption, and emphasize the desirability of removing as much of the contrast medium as possible after myelography or at operation. *A. Orley*

710. **Angiocardiography in the Preoperative Diagnosis of Mitral Stenosis and Insufficiency**

J. G. MCAFEE, T. F. HILBISH, and K. R. STEWART. *Radiology* [*Radiology*] **67**, 321–332, Sept., 1956. 7 figs.

Angiocardiography as performed with present technics was not a reliable procedure for distinguishing between mitral stenosis and insufficiency in 32 cases proved by surgery. The diagnostic accuracy was poorer than that of conventional clinical methods. Both " false positive " and " false negative " diagnoses of mitral stenosis were made. In this, as in other unselected series, cases with stenosis predominated. The problem of selecting the small minority of cases with predominant insufficiency has not been solved by angiocardiography.

No difference in the " opacification pattern " of the left atrium and ventricle was observed in stenosis and insufficiency which could not be explained on the basis of chamber size and cardiac phase. The prolonged opacification of the left atrium seen in mitral disease is due to its large size and the generalized slowing of the circulation. In the absence of shunts, the output (volume per unit time) in all chambers of the heart remains equal; there is no specific " hold-up " of the contrast medium in the left atrium by a stenotic mitral valve.

Angiocardiography is of value in demonstrating the size and position of the cardiac chambers, but this can usually be assessed by ordinary roentgenographic means. Left ventricular enlargement was demonstrated in only 2 out of 5 cases of proved " pure " mitral insufficiency. It may be possible in the future to visualize the mitral valve orifice by selective angiocardiography performed through a direct left atrial puncture.—[Authors' summary.]

711. **Radiologic Diagnosis of Hiatus Hernia**

L. K. SYCAMORE. *Gastroenterology* [*Gastroenterology*] **31**, 169–189, Aug., 1956. 20 figs., 23 refs.

It is apparent that the anatomy and physiology of the esophagogastric junction are as yet incompletely understood, and many elements of the problem remain in dispute. As a corollary, the significance of many of the radiologic appearances in this area has not been determined, and the conclusions of today may be called in question by further evidence adduced tomorrow. The diagnosis or exclusion of hiatus hernia by radiologic examination, therefore, may at times be difficult. Certain findings, if present, are helpful. A coarse, irregular mucosal pattern above the diaphragm, except in a vestibule, usually indicates hernia; fine parallel lines, however, are less reliable as an indication of a normal lower esophagus. Reflux of barium upward as a normal peristaltic wave descends, or emptying of barium into the stomach during sustained inspiration are evidences of a normal ampulla. One of the most important findings in support of the diagnosis of hernia is the demonstration of a wide hiatus. Retrograde filling of the pouch from the stomach, a broad vertical notch, or a rounded circular groove furnish contributory evidence in favor of hernia.

Continued observation and experimentation are necessary before the varied elements of this interesting problem can be assembled in a complete whole.—[Author's summary.]

712. **On the Relative Merits of the Oral and Intravenous Methods of Cholegraphy**

D. STENHOUSE. *British Journal of Radiology* [*Brit. J. Radiol.*] **29**, 498–503, Sept., 1956. 5 figs., 8 refs.

In order to assess the relative merits of the oral and intravenous methods of cholegraphy, 100 unselected cases referred for *x*-ray examination of the gall bladder have been examined by both methods, using the compounds " telepaque " and " biligrafin " respectively. In the detection of stones in the gall bladder, telepaque is more accurate than biligrafin. Absence of the gall bladder shadow after biligrafin, provided the ducts are visualised, is reliable evidence of gall bladder disease; after telepaque it may be due to other factors, such as failure of absorption. Biligrafin demonstrates the bile ducts more often and more clearly than telepaque.

It is concluded that the two methods are complementary. A practical scheme is to reserve the intravenous method for those cases in which the oral method has failed to demonstrate the gall bladder or bile ducts.—[Author's summary.]

History of Medicine

713. **The Genesis of State Medicine in Ireland**
K. DEWHURST. *Irish Journal of Medical Science* [*Irish J. med. Sci.*] 365–384, No. 368, Aug., 1956. 2 figs., 27 refs.

The development of state medicine has always been stimulated in times of war, and the history of public health in Ireland confirms this. The Irish rebellion of 1641 and the period of Catholic supremacy under James II were followed by violent Protestant reprisals and strong English government, but during this, the most turbulent century in the country's history, the contributions of a few learned men provided the foundation of Irish state medicine.

The pioneer in this work was Dr. William Petty, a reader in anatomy at Oxford and one of the first members of the Royal Society, who landed in Ireland in 1652 as Physician-General to Cromwell's army. After proving his ability as an administrator, he began to pursue his favourite interest of statistical analysis. He urged the establishment of a statistical office for the accurate census of the population and valuation of property. For some years bills of mortality had been collected in Dublin, and in 1683 Petty published observations on these bills in which he suggested improvements in their compilation. In particular, he specified 24 causes of death to replace the many fanciful diagnoses of the unskilled, and pointed out that religious differences caused inaccuracies in the burial rate.

In England at this time the Baconian philosophy of scientific inquiry was being seriously applied in many fields. One line of research was the Hippocratic theory, echoed by Sydenham in his *Methodus Curandi Febres*, 1666, that the virulence of an epidemic and the nature of a disease varied with the prevailing atmosphere at the time. Thus, efforts were made to show that variations in the weather were reflected in the mortality rate. Among those who worked on this problem were Sir Christopher Wren, Robert Boyle, and John Locke. Questions from Locke to Dr. Willoughby and to Sir Patrick Dun of the Dublin College of Physicians and the replies thereto provide us with a complete survey of state medicine in Ireland in the late 17th century.

These questions dealt with the statistics in the Dublin bills of mortality, covering the period 1681–91; the climate and diseases of Ireland; opinions concerning Jesuit's bark [cinchona] and Dr. Sydenham's theories; and conditions of medical education and practice in Ireland. Willoughby's replies are full of interesting detail, with discerning and often amusing interpretations. Although smallpox was then on the wane, the " feaver " (typhus) was on the increase, and this Willoughby rightly attributed to the invading army. He refused to comment on the infant death rate, because the figures were derived entirely from deaths from unknown causes. Similarly the figures for the birth rate were inaccurate, because the many Nonconformists and Catholics did not appear on the Church registers. The high death rate in town as compared with country was noted and attributed to crowded living conditions. The female population was estimated to be slightly lower than the male, and this fact was ingeniously used to justify simultaneously monogamy, private property, and celibacy of the clergy. The statistics for dysentery showed a decrease, due, Willoughby considered, to the drainage carried out by the English settlers. He suggested that the good work should be carried on, compulsorily if necessary, by the State, and that more husbandry and new industries should be encouraged, the required labour being drawn from the occupying troops. Although smallpox and typhus infections were most virulent from June to September, Willoughby admitted that he could find no pattern to prove the influence of climate on disease generally. His description of the Irish weather is detailed and vivid. He is full of praise for the bark in the treatment of intermittent fevers, but is more cautious concerning Sydenham's theories of disease. In the field of education, he applauded the schools of London and Leyden, and maintained that the Irish regulation of apothecaries and surgeons was adequate.

The letters of Sir Patrick Dun, written in 1695 and 1698, deal with the Dublin bills of mortality, the role of French wines in causing fevers, and the difficulty of suppressing irregular practitioners. They were probably part of a larger correspondence with Locke and other members of the Royal Society. Dun himself was a founder of the Dublin Philosophical Society.

F. M. Sutherland

714. **The Three Alexander Monros and the Foundation of the Edinburgh Medical School**
D. GUTHRIE. *Journal of the Royal College of Surgeons of Edinburgh* [*J. roy. Coll. Surg. Edinb.*] **2**, 24–34, Sept., 1956. 6 figs., 31 refs.

The author points out that although the three Alexander Monros played a large part in the history of the Edinburgh Medical School, the initial inspiration came from John Monro, the youngest son of Sir Alexander Monro, who fought in the King's forces at the battle of Worcester in 1652. John Monro (1670–1740) served as an Army surgeon in the Low Countries in 1692, and was so impressed with what he saw on a visit to the medical school at Leyden that he determined that Edinburgh should have a school of like merit. He gave his only son, Alexander (1697–1767), an excellent education by sending him to study medicine in London, Paris, and Leyden, and succeeded in getting him installed as professor of anatomy in Edinburgh at the early age of 23. Alexander Primus proved to be an excellent teacher, who greatly helped in the foundation of the Edinburgh Faculty of Medicine (1726). He and his father also helped to provide clinical experience for the

students by assisting in the establishment of the " Little House " (1729) and the " Surgeon's Hospital " (1736), which ultimately led to the opening of the Infirmary in Drummond Street in 1741. The Surgical Hospital where Syme and Lister worked was not opened till 1832. Alexander Primus lectured until 1758, when he retired in favour of his son Alexander, known as Secundus. The second Alexander Monro was also a famous teacher, whose reputation equalled if it did not surpass, that of his father; during his long reign as professor he taught more than 14,000 students, many of whom became well-known as teachers in Britain and America. The third Alexander Monro (1773–1859) was the son of Alexander Secundus and succeeded his father in 1808. Although he remained in office until 1846 he was not the equal of either his father or grandfather. On his retirement the long professorial reign of the Monros ceased. Alexander Tertius had 12 children, one of whom, David, the fourth son, emigrated to New Zealand, became a prominent polifician, and attained the dignity of knighthood. Many of the manuscripts and books belonging to the Monros came into the hands of Sir David, and these were passed on to his son-in-law, Sir James Hector, whose son (Dr. Monro Hector) handed them over to the Medical School at Dunedin in 1929. The author of the present paper had the privilege of examining these treasures on the occasion of a recent visit to New Zealand. *Zachary Cope*

715. **Sir William Gull and Psychiatry**

R. A. HUNTER and H. P. GREENBERG. *Guy's Hospital Reports* [*Guy's Hosp. Rep.*] **105**, 361–375, 1956. 1 fig., 30 refs.

Sir William Gull, physician to Queen Victoria and the Prince of Wales, was pre-eminent in his profession and at the same time very freely critized by his colleagues. This can be attributed to his belief in the curative power of nature, to his objection to the haphazard treatment of symptoms by drugs, and, above all, to " his remarkable insight into and sympathy with his patients ". His interest in psychiatry and his psychological approach to medicine can be traced to the teaching of John Conolly, Superintendent of the Middlesex County Lunatic Asylum at Hanwell.

In England clinical instruction on psychiatric patients began in 1753, when William Battie at St. Luke's Hospital for Lunatics gave demonstrations. It soon lapsed, however, and was not again available until 1842, when it was revived by Conolly at Hanwell. Conolly made the proper study of insanity possible by his institution of the system of non-restraint. Gull, possibly encouraged by Thomas Hodgkin, was an early student at Hanwell and recorded vivid impressions of the work done there. In 1843 he was able to put the lessons into practice when he was appointed medical superintendent of the lunatics at Guy's Hospital. In Guy's will there was provision for the care of 20 incurable lunatics, and in 1728 the first patients were admitted to the hospital. Evidence before the House of Commons Committee on the State of Madhouses in England (1815) showed that at Guy's the patients were kept reasonably clean, but that there was a considerable degree of restraint, no provision was made for classification, and heating and ventilation were inadequate. In 1840 the Charity Commissioners could report no improvement; indeed, they compared conditions at Guy's unfavourably with those at Bethlem and Hanwell. With Gull's appointment reforms were immediately instituted, and by 1851 the comfort of patients was materially increased, occupations were being provided for them, and all mechanical restraint had been abolished. By 1853 Gull had resigned, and by 1861 the hospital authorities had closed the lunatic wards which they had always regarded as a dubious asset.

Gull followed Conolly not only in abolishing restraint of the insane but also in determined opposition to the use of many physical remedies—for example, bleeding, vomiting, purging, and blistering. He believed implicitly that it was more important to study than to explain the phenomena of disease, and that the symptomatic treatment of half-understood diseases was highly dangerous. His paper on the mint-water treatment of rheumatic fever was intended to show that patients improved as well without medicine as when they were given drugs. Unfortunately the prevailing obsession with drug therapy was such that as a result " mint-water treatment became fashionable for rheumatic fever ".

Gull believed that in the patient's mind lay the origin of much illness. This psyehosomatic approach to disease is revealed in a number of his writings. In 1868, with Edmund Anstie, he published an account of hypochondriasis in which he emphasized that it was a mental disorder, that the sufferings of the patient were very real, and that treatment of symptoms was to be avoided. He described anorexia nervosa in 1874 and 1888, attributing the loss of appetite to a morbid mental state and recommending appropriate treatment. Gull's published works included two clinical psychiatric papers, one describing cases of trichobezoar and the other a case of melancholia. Thus in his writings as well as in his work in the lunatic wards at Guy's, Gull showed his psychological approach to medicine. His influence extended to the next generation of physicians, personified in Samuel Wilks. *F. M. Sutherland*

716. **Charles Turner Thackrah and Industrial Dermatosis**

F. F. HELLIER. *Transactions of the St. John's Hospital Dermatological Society* [*Trans. St. John's Hosp. derm. Soc.* (*Lond.*)] 1–2, No. 36, 1956. 1 fig.

Charles Turner Thackrah, an apothecary who practised in Leeds from 1816 until his death at the early age of 38, is generally regarded as the " father of British industrial medicine ". In 1831 he published a pamphlet entitled: " The effects of the principal arts, trades and professions, and of civic states and habits of living on health and longevity with particular reference to the trades and manufactures of Leeds: and suggestions for the removal of many of the agents which produce disease and shorten the duration of life ". Encouraged by the favourable reception of his work, he extended his studies and published the results in a second edition which

appeared in 1832. The present paper from the Leeds Medical School, of which Thackrah was a founder, gives a brief biographical sketch of the author and comments briefly on occupational skin diseases as recorded in the book.

An excellent reproduction of the head from the half-length oil painting of Thackrah which hangs in the Leeds Medical School is included as a frontispiece to the paper. *A. Meiklejohn*

717. **Mozart as a Patient.** (Mozart als Patient)
D. KERNER. *Schweizerische Medizinische Wochenschrift* [*Schweiz. med. Wschr.*] **86**, 1343–1346, Nov. 24, 1956. 1 fig., bibliography.

718. **Miss Florence Nightingale and the Doctors**
ZACHARY COPE. *Proceedings of the Royal Society of Medicine* [*Proc. roy. Soc. Med.*] **49**, 907–914, Nov., 1956.

719. **Nikolai Ivanovich Pirogov—Surgeon, Anatomist, Educator**
G. HALPERIN. *Bulletin of the History of Medicine* [*Bull. Hist. Med.*] **30**, 347–355, July–Aug., 1956. 3 refs.

This paper provides a sympathetic account of the life of that remarkable Russian surgeon, Pirogov, without calling on any fresh sources of information. His entry to Moscow University at the age of 14, his qualification at 17 without having performed even a dissection, and his postgraduate training at Dorpat, where he acquired an interest in surgery under the able Professor Moyer, are described. Moyer found Pirogov to be a brilliant student and gave him every encouragement, and, when Pirogov returned from 2 years' study in Berlin, recommended him as his successor in the professorship. Pirogov quickly overcame the early dislike which the German-speaking students of Dorpat could be expected to show toward a Russian, and gained their respect and affection. At the age of 30, despite much opposition, he was appointed professor of surgery at St. Petersburg, whose Medico-chirurgical Institute, controlled by the Ministry of Internal Affairs, was at a very low ebb. His fame rapidly spread, although many of his colleagues failed to understand his attitude towards fees, for he never demanded any payment, but contented himself with what his patients offered him for his services.

Pirogov's part in the introduction of ether anaesthesia into Europe in 1847 and his efforts to improve medical services during the Crimean War are briefly mentioned. [See also *Bull. N.Y. Acad. Med.*, 1955, **31**, 519; *Abstracts of World Medicine*, 1956, **19**, 176.] Disgust with the intrigues in the Military Academy forced him to resign, and he turned his attention to education, being appointed head of the education system in southern Russia. The diverse population of this part of the country encouraged him in his support of the rights of national minorities and, on the other hand, of the belief that in science there is no room for national prejudices. He favoured a free press and actively campaigned for its establishment. His outstanding publications were the dissertation on ligation of the aorta (in Latin), a description of inguinal hernia, his "Annals", in which in typically Russian fashion he published his errors, and his "Atlas of Topographical Anatomy". For this last work he obtained much of his material from the study of sections of frozen cadavers—proof of his inventive genius.

Pirogov died at his country estate in 1881 from a malignant growth of the mouth. Billroth had told him that it was not malignant and would resolve spontaneously, declaring after Pirogov had died that he knew perfectly well that it was malignant, but wished to spare him from worry and meddlesome surgery.

Basil Haigh

720. **Humphrey Lhuyd (1527–1568). A Sixteenth Century Welsh Physician**
G. P. JONES. *Proceedings of the Royal Society of Medicine* [*Proc. roy. Soc. Med.*] **49**, 521–528, Aug., 1956. 1 fig., 28 refs.

Humphrey Lhuyd of Denbigh was one of the leaders of the intense literary revival which took place in Wales in the latter half of the sixteenth century and played an influential part in making Welsh literature and antiquities more widely known among scholars and historians, by whom the ancient Welsh chronicles had hitherto been largely ignored. Born in 1527, Lhuyd studied medicine at Oxford and had already published translations of the *Thesaurus Pauperum* of Petrus Hispanus and of John Vassay's book on uroscopy when, in 1553, he became private physician to Henry Fitzalan, twelfth Earl of Arundel and a leader of the Catholic minority. A typical product of the Renaissance, Arundel was a scholar and antiquarian who had built up an important library at his palace of Nonsuch, near Epsom, which was also one of the most important centres of political activity and intrigue of the period. Here Lhuyd joined Arundel, his son Henry Maltravers, and his son-in-law Lumley (who later endowed the Lumleian lectures of the Royal College of Physicians) in antiquarian studies and laid the foundations of his historical learning. In 1563 he returned to Denbigh, where he devoted himself largely to literary and historical pursuits, though he still continued the practice of medicine and was also Member of Parliament for the borough of Denbigh until his death in 1568 at the age of 40.

Lhuyd's reputation as a historian rests chiefly on his *Cronica Walliae*, an English version of the Welsh *Chronicle of the Princes*, his *De Mona Druidum Insula*, and his *Commentarioli Britannicae Descriptionis Fragmentum*, notes on the history of Britain made on his deathbed for his friend Abraham Ortelius, the geographer (to whom he also sent two maps, of Wales and of England and Wales, which are of prime importance in British cartography). In all three works he attacked historians such as Polydore and Hector Boethius for their neglect of the ancient Welsh sources and for their historical prejudice and ignorance.

Donald Crowther

721. **Dr. Jonathan Odell—Tory Satirist**
F. B. ROGERS. *Transactions and Studies of the College of Physicians of Philadelphia* [*Trans. Stud. Coll. Phys. Philad.*] **24**, 70–75, Aug., 1956. 12 refs.